MONOGRAPHS

JOURNAL OF THE NATIONAL CANCER INSTITUTE

NATIONAL CANCER INSTITUTE

*ICCCR International Conference on Cancer Prevention: Facts, Maybes & Rumors*

**1992**
*Number 12*

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# ICCCR International Conference on Cancer Prevention: Facts, Maybes & Rumors

Proceedings of a Conference
Held at the
National Institutes of Health
Bethesda, Maryland
February 12–13, 1991

**The International Council for Coordinating Cancer Research (ICCCR)**

The ICCCR is a non-profit organization that acts as a catalyst in promoting collaboration between cancer research scientists worldwide in an effort to accelerate methods for the prevention and control of cancer.

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*ICCCR International Conference on Cancer Prevention: Facts, Maybes & Rumors* **1992** *Number 12*

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## MESSAGE FROM THE STEERING COMMITTEE

Since 1985, the International Council for Coordinating Cancer Research (ICCCR) together with the French Association for Research on Cancer (ARC), the National Institutes of Health (NIH), and the National Cancer Institute (NCI) have sponsored numerous conferences and symposia designed to provide a forum to discuss specific research findings, expand international communication, and create research networks between scientists.

In 1991, ICCCR hosted the first International Conference on Cancer Prevention: Facts, Maybes & Rumors. The advances in medical research over the past several decades have created tremendous progress, particularly in the area of molecular biology. It was the initial integration of molecular biology into prevention research as well as the potential for future exploration that offered a uniqueness to the concept of this international prevention conference. The steering committee felt that it was imperative to bring the international research community a concise picture of the current foundation of prevention research and provide the opportunity for prevention experts to collaboratively define a research agenda.

One specific goal of the conference was to delineate some basic perspectives about cancer causation: establish the FACTS that have been scientifically proven; the MAYBES that are intriguing and under active examination; and the power RUMORS that are unproven and often distort media and public opinion about cancer. In addition, this conference allowed for discussions of how the research community can mobilize its knowledge base and expertise in shaping health care policy.

The conference was exciting and offered the opportunity to define a research agenda for the next decade.

## IN MEMORIAM — DR. JOSEPH W. CULLEN

The cancer community lost one of its most influential leaders with the sudden death of Joseph W. Cullen on November 24, 1990. It is ironic that the cause of his death, a malignant brain tumor, was the very disease that he had dedicated his life to eradicating. Dr. Cullen was a pioneer in prevention, a man who had a major role in charting its course, and he has left a rich legacy to those of us that continue our efforts in the area of cancer prevention.

Dr. Cullen was a key member of the Steering Committee for this first International Conference on Prevention. He was to have presented a paper describing the Effectiveness of Prevention Programs and to have chaired the Roundtable on Tobacco.

At the time of his death, Dr. Cullen was director of the AMC Cancer Research Center in Denver. However, many of us had the privilege of working with him during his tenure at the National Cancer Institute. While serving as Deputy Director of the Division of Cancer Prevention and Control, he developed the Smoking, Tobacco & Cancer program which has been acknowledged to have positively affected the lives of millions.

In a very non-poetic but genuine statement, he was one of the nicest guys on the face of the earth, with an optimism and excitement which will be sorely missed. It is only appropriate then to dedicate this conference to the memory of our colleague and friend, Joe Cullen.

# Introduction

**Jacques Crozemarie**[1]

To disseminate critical information about cancer research and expand the international network of basic and clinical research, the International Council for Coordinating Cancer Research (ICCCR) has hosted numerous international conferences since 1985 in collaboration with the French Association for Research on Cancer, the National Institutes of Health, and the National Cancer Institute. Recently, the ICCCR board of directors endorsed a decision to focus a significant portion of their efforts toward cancer prevention. This decision was based on a belief that prevention of cancers is crucial in effectively controlling the global cancer epidemic. Cancer prevention research priorities are underfunded, and cancer prevention lacked a clear approach to increase its visibility. Therefore, the ICCCR developed a cancer prevention and control position statement.

The conference on cancer prevention, "Facts, Maybes, and Rumors," challenged researchers to weigh the evidence presented by international experts in the area of prevention and to look for future international research priorities in cancer prevention. It is hoped that the conference helped to decide the future direction of cancer prevention from an international perspective.

The statistics of this epidemic must be considered. During the 2-day conference, 2100 people died of cancer. In the United States alone, over 1 million will be diagnosed with cancer this year and, worldwide, over 7 million people are diagnosed with cancer each year. It is my belief that prevention of cancer is one of the most effective tools for dealing with this epidemic.

Most people have known someone who has been afflicted with cancer. The death of our friend and colleague, Joe Cullen, president of the AMC Cancer Research Center in Denver, is such an example. Here was a man who had dedicated his life and career to closing the chapter on cancer. Cancer knows no social, economic, or educational boundaries; it strikes the rich, poor, young, and old. Like Joe, many are people in the prime of their life who are making substantial contributions.

Cigarette smoking alone accounts for about 30% of all cancer in the United States, and alcohol consumption and sexually transmitted diseases may cause an additional 10%. Diet is a highly variable factor, and its importance varies according to geographic and ethnic backgrounds. Factors associated with diet are estimated to contribute to about 35% of all human cancers. Occupational exposure to various chemicals used in industrial processes probably accounts for some cancers, and the total contribution of environmental pollution, including toxic-waste disposal, is difficult to estimate. Comparisons of populations and evidence from experimental and epidemiological studies suggest that 80%–90% of human cancers are determined environmentally and may be avoidable.

The question is where to look for the causes that account for these cancers believed to be preventable. The concept of prevention is fundamental to fighting cancer. Protecting the environment should be a first step toward prevention of cancer. Damage to the environment is caused by factors that can also affect the microcosm of family and individuals. Active and passive smoking are two of the most striking examples. I will carry these messages to Rio de Janeiro for the World Conference on Environment and Development organized by the United Nations.

The environmental factors that can be linked to cancer in humans include smoking, life-style, diet, the sun's $\beta$-rays, pollution, and radiation. Therefore, to prevent cancer, it is necessary to consider environmental problems and attempt to solve these problems.

The threat that chemical and atmospheric pollution presents merits attention by oncologists. Theoretically, global warming can increase and extend concentrations of ozone in urban areas. This increase is a health risk. The urban atmospheric environment also contains numerous organic carcinogens. Some of these substances are produced or decomposed by chemical reactions in the air, and concentrations of pollutants can be modified by global warming and an increase in ultraviolet $\beta$-rays. Global warming could thus influence the concentration of many organic pollutants in the environment, which could translate into a change in exposure by humans. Environmental impact studies are crucial for an economic policy. Moreover, the concept of public health and cancer should be involved in these studies.

The international research community must embrace and reinforce a balanced research agenda that includes cancer prevention as a pivotal element. A comprehensive prevention research agenda must draw on many fundamental aspects of cancer research, basic research, epidemiology, and cancer prevention and control. By eliminating many of the key environmental causes of cancer, major advances can be made in the fight against cancer. Prevention and control programs should serve as the bridge between knowledge derived from basic and clinical re-

[1] International Council for Coordinating Cancer Research, French Association for Research on Cancer, and French National Science Research Center, 7, rue Guy Mocquet, B.P. 3, 94801 Villejuif, France.

search programs and its application to clinical and public health settings.

There is agreement among scientists that by 2000, 75% of all cancers will be preventable. Researchers worldwide have been working on the cures for different types of cancers, and their efforts have been successful. A significant percentage of cancers are due to nutritional factors; however, the results are nothing compared with what could be achieved if people stopped smoking. Despite these positive efforts, many initiatives have not been taken against tobacco, alcohol, food, and chemical industries because of strong lobbies. Significant changes must be made if the 2000 goal is to be met.

The following areas must be investigated:

- The impact of smoking, tobacco use, and exposure to smoking in the environment
- Dietary factors that contribute to the development of cancer
- The role of alcohol consumption, nutrition, and tobacco use in the development of cancer
- Development of chemoprevention agents
- Epidemiology of the impact of environmental carcinogens
- Effects of ultraviolet exposure
- Behavior modification effective in cancer control

An international audience of experts should be tapped to discern the scientific facts, the maybes that merit further investigation, and the rumors that distort the perception and understanding of cancer by the public and the media. These experts must respond to the challenge and create an international research agenda that will guide us through the next decade.

# Welcome Address

**Vincent T. DeVita, Jr.**[1]

The International Council for Coordinating Cancer Research (ICCCR) is a nonprofit organization devoted to fostering international collaboration in cancer research. It is an organization that was created to focus on research projects of international origin, largely because whenever a project is conducted in two different nations, the funding often falls into default because neither side necessarily claims primary responsibility for supporting the research.

With the support of our scientific advisory board, the ICCCR solicits international research projects and facilitates funding. Over the past 2.5 years, we have funded $5 million worth of projects on a wide range of subjects. However, the board recently decided to change the direction of the organization to make it focus almost exclusively on cancer prevention research.

Prevention research is chronically underfunded despite the fact that many of the prevention studies have had international origins. Population studies and migration studies, the data bases that we use to develop new concepts, are really international data bases.

These proceedings should be viewed as a way of announcing the intention of the ICCCR to put its shoulder to the prevention wheel and of attracting attention to the prevention community so that projects can be presented if they are in need of our support.

Second, we intend to export the message of this conference. Plans are under way for a second international conference in Europe, where the concerns and attitudes about prevention are somewhat different from those in the United States. Some of these differences are evident throughout the articles in this monograph. Although we may not be able to export the entire message of this conference, the concept of examining prevention in terms of facts, maybes, and rumors is worth exploring on a wider scale and on an ongoing basis.

[1] International Council for Coordinating Cancer Research, 555 Madison Ave., Suite 2900, New York, NY 10022.

To conclude, we are approaching the 20th anniversary of the National Cancer Program (NCP); thus, it is fitting for us to evaluate our progress with cancer prevention. The NCP has lost momentum, largely because of the short attention span of Congress. When the National Cancer Act was passed in 1971, there was great enthusiasm in Congress; however, it has been difficult to keep our legislators focused on a project that was clear to scientists from the beginning would take 20–30 years of hard work before progress would be apparent.

Finally, the investment in molecular biology that has been made over the past two decades is paying off handsomely, particularly by providing, for the first time, a real opportunity to prevent cancer. Fifty percent of all molecular biology in the United States is supported by the National Cancer Institute (NCI), despite the fact that the NCI budget is only about 23% of the total National Institutes of Health budget. As a result, we now have information at the molecular level of the genetic risk factors that will make prevention studies, including those that are controversial, much easier because they will probably involve smaller and more clearly delineated populations.

Prevention research, as I was constantly reminded as director of the NCI, is risky and controversial. It is risky because of its long-term aspect. Unfortunately, someone whose roots are in treatment receives gratitude for successful treatment; interest in prevention does not elicit such gratitude, because a person who does not get a disease is often unaware—or does not remember—the preventive measures involved.

Prevention and prevention research are also controversial in terms of public perception, because we have varying levels of confidence in and assessment of our data; hence, the facts, maybes, and rumors. Finally, funding in the NCP for what always has been perceived as the effector arm of cancer prevention, the Cancer Prevention and Control Program, has been meager. Therefore, these proceedings chart a course for the actions of the international prevention community toward acquiring the funds to bridge our knowledge in the basic sciences with critical social and intervention programs to translate the fruit of our research efforts.

# Keynote Address

**C. Everett Koop**[1]

The International Coordinating Council for Cancer Research (ICCCR) should be recognized for supporting this conference, because cancer prevention is a crucial priority in our effort to control and eradicate cancer on a national and international basis.

One person who was critical to the planning of this conference was Joe Cullen, whose enthusiasm carried me far beyond my original intended purpose in many things that I did as surgeon general.

In preparation for the publicity for this meeting, I had a telephone interview with a magazine editor who startled me with a series of personal questions. She did not know what to do about her children, because she lives on a street that has a step-down transformer and cannot let them play outside. She cannot send them to the park either, because they might get Lyme disease from ticks in the grass. She also is not happy about sending them to school because she knows there is asbestos in the walls. I began to wonder whether she had read anything yet about amalgam fillings or knew about some of the things that people said about pesticides on broccoli. Instead, I shocked her; when she asked me about my sleeping habits, I said that I slept contentedly under an electric blanket every night. That bothered her so much that it is probably the reason why she did not take the time to report this conference in her journal.

When the steering committee discussed the content of this meeting, we all wanted to deliver the message that some cancers can be prevented. We also wanted to take the fear out of people thinking about it. Tomorrow's headlines could unnecessarily depress the reader about statistics on cancer deaths or they could create undue optimism about some exaggerated claim. The aim of this conference was perhaps to oversimplify the differences between and among facts, maybes, and rumors; in any event, we will be ahead of the game because this monograph contains some important suggestions and goals for research.

I would like to depart from cancer and from this particular conference and its specifics and deal more generally with the field of public health, although what I have to say about public health in reference to this conference should not be minimized. Public health professionals are really great educators if the goal of education is the accumulation of knowledge. On the other hand, if the goal of education in public health is to change behavior, then we, as public health educators, have a lot to learn.

I had a personal encounter with the AIDS epidemic that I think illustrates this good news/bad news scenario. In 1986, we knew that 14- to 17-year-olds knew almost nothing about AIDS. We had tested them with polls, and their knowledge was down around 60%; thus, for 2 years we targeted 14- to 17-year-olds. They had never heard such explicit talk about how to prevent sexually transmitted diseases. After our targeted education campaigns, we polled them again, and we had indeed educated them. They now knew about 88% of the subject material associated with AIDS, but there was absolutely no behavioral change. As a matter of fact, in 1988, in that same age-group, penicillin-resistant gonorrhea and infectious syphilis climbed at rates that we had not seen in the US for 16 years.

I came to the position of surgeon general after almost 40 years of a career in pediatric surgery; during those years, I had looked at medical problems and tried to solve them with the skill of my own two hands. Like most scientists and physicians, I was a problem solver. I suspect that many participants at this conference consider themselves problem solvers, people to whom others have come when they want something done, when they want something fixed. I subconsciously thought that was what health care and medical care were really all about; I think that most physicians hold the natural bias that health care is the sum of the things done to "patch up" patients. To a certain extent, I guess it is; but not entirely—certainly it is going to be less so in the future. This is one of the chief lessons I learned as your surgeon general: virtually every major health issue that I had to deal with had at its heart the way that people behave—the way they behave toward themselves, and the way they behave toward others.

Let me list a handful of current medical issues; think of what these behaviors do in reference to individuals themselves, to those whom they love, and to strangers: smoking; alcohol abuse; unwanted pregnancies; child abuse and other forms of family violence; AIDS; and, for the purpose of this discussion, cancer. At the base of each of these painful, tragic, destructive, and preventable health problems is an equally tragic and destructive human behavior. This is not an easy subject to discuss in a democracy because we pride ourselves on letting the individual make the decision as to what he or she wants out of life. Society has agreed, at least so far, to pay almost any price to keep that part of our social compact alive and well. Thus, a great deal of time, effort, and human and material resources are put into scientific discovery, vaccine

[1] International Council for Coordinating Cancer Research, 555 Madison Ave., Suite 2900, New York, NY 10022.

research and development, drug development, and physical and mental therapies of all kinds. However, these kinds of medical and public health responses are, indeed, after the fact. We then turn to large, broad-brush kinds of public education programs to do the tough, long-term job of correcting hazardous, high-risk human behavior—but also after the fact. For example, we are concerned, and rightly so, about the safety of health workers in regard to diseases like hepatitis B and AIDS.

We have two major instruments to work with: a relatively recent hepatitis B vaccine and the individual health worker. However, the vaccine works only if the individual health worker and his or her supervisor have the good sense and the enlightened self-interest to want the protection of the hepatitis vaccine now. Furthermore, we must rely solely on the judgment and personal behavior of individual health workers for their protection against the AIDS virus. I believe that the people in our health-care work force are good and responsible; they are also people who are caught, as are the rest of us, in the shifting tides of national culture and common values.

There is a direct relationship from the 1960s, when many constraints in our society disappeared, especially concerning experimentation with drugs and sex; to the 1970s, when such experimentation became widespread among young people in this country; and, finally, to the 1980s, when the tragic results of much of this behavior was clearly seen in statistics.

We are making excellent progress in many areas of public health and medicine, eg, hypertension screening; organ transplantation; and cancer detection, control, and prevention. In many other areas, however, we seem to be running in place, if not falling behind. Much time has been spent in the past few years posting the weekly tallies of drug overdose deaths, children having children, victims of the new epidemic of syphilis, the escalating number of strains of gonorrhea resistant to antibiotics, and the expanding caseload of people who were incubating the AIDS virus until just the right opportunistic disease came along. The statistics are not good. Far too many people in our society have fallen victim to debilitating and deadly diseases, and we suspect that the worst numbers are not in yesterday's files but rather may show up in future tally sheets.

The problem begins early in our schools and in the privacy of our homes, places where public health authorities and scientific experts are not supposed to go. However, those places are, indeed, the frontiers in medicine and public health, where a whole new generation of Americans is developing. We need to be bolder when we discuss behavior and its consequences. The problems faced by America's underclass stem less from inadequate government programs than from disastrous personal behavior. We need to take parenting much more seriously, especially the part of parenting that requires parents to be responsible for their children's behavior. Our society gets more upset today about scientific experiments on cats than it does about children being raised by inadequate or absent parents.

As an ex-health officer, I am discouraged that the public health education directed toward teenagers did not result in a behavior change that reduced sexually transmitted diseases. We know that teenagers, in addition to thinking they are immortal, are natural risk takers; they do not change their behavior out of fear of natural consequences that seem remote. We need to take another approach, one that is not merely a new technique of teaching. It may lie in the age of the first presentation of that teaching, enforcing it for a lifetime and adjusting a curriculum and the art of teaching to the age of the learner.

Concerned Americans must exert leadership, not only in established positions but also in formal relationships in everyday life, to lead the way to a new level of personal responsibility. There is a special challenge before us at this time in our history when personal freedom and responsibility are in a somewhat uneasy balance. We need to find ways, effective yet consistent with American tradition, to help young people—schoolchildren—develop a healthy sense of their own personal worth and a genuine appreciation of the worth of everyone else. This must start when school starts. Proper teaching is too important to be left to the schools alone, and it cannot be left to schools and parents alone either. It is the responsibility of all relatives, in short, the entire adult community. They must take seriously their personal responsibility for younger generations, a responsibility that includes both precept and example.

We need to emphasize, at the earliest age possible, the moral imperative of basic human dignity and basic human decency. Stern warnings about behavior can lose their effectiveness if they are used too often. We must affirm a new sense of respect for each human life in the next generations, and they must see the same values in us. It is a common human trait, or perhaps an instinct, to protect the things and the people we value. We need to exploit that trait more often, and we should do it in the name of public health and reinforce it especially among our children.

The future holds a partnership in homes, schools, churches, and civic groups, teaching us to take charge of our health now in regard to smoking, alcohol, and drugs. The understanding of choice in behavior would be a tremendous and fundamental part of such a curriculum if it is applied to diet, exercise, discipline, and incentives leading to better physical fitness than we have among children in this country. Certainly, wellness would be one of the hallmarks of such a program.

If we teach human development in a family context—stressing kind, loving, caring, and considerate relationships—I think we can raise a generation of preteens to be less sexually active, or to postpone sexual activity, in a way that has not been possible with the present cohort of teenagers. If we set this as a national goal, we might be doing the most important thing, making the most important contribution, to the health of all Americans who are to come of age in this next century.

# Keynote Address: Cancer Prevention

**Peter Greenwald**[1]

**ABSTRACT—Life-style factors that have a major impact on cancer risk are smoking, alcohol consumption, and diet. Current evidence suggests that dietary fat is an etiologic factor for colorectal and postmenopausal breast cancer and that foods high in dietary fiber may be beneficial against colorectal cancer. Clinical prevention trials, augmented by molecular and biological marker studies, will provide new knowledge for diet modification and chemoprevention. These studies are likely to influence the scope of oncology and public health practices of the future. [J Natl Cancer Inst Monogr 12:9–14, 1992]**

The role of life-style factors in the development of cancer has become increasingly evident as cancer research has progressed. Many studies have demonstrated that the most important factors for cancer risk are smoking, alcohol consumption, and diet. In the United States, conclusive evidence of the association between cigarette smoking and lung cancer was first published in the 1950s (*1, 2, 3*). Since the publication of the Surgeon General's Report in 1964 (*4*), compelling evidence indicates that cigarette smoking is a major cause of cancers of the lung, larynx, oral cavity, and esophagus; smoking is also a contributory factor in the development of cancers of the bladder, pancreas, and kidney. Current research evidence indicates that tobacco contributes to 30% of all cancer deaths.

With the exception of smoking, dietary habits are the most significant life-style factor in cancer risk, accounting for possibly 35% of cancer incidence (*5, 6*). The development and implementation of nutrition-based cancer intervention strategies targeted at the general population or specific high-risk groups can have a major impact on public health.

The concept of diet as a possible etiologic factor has received momentum from basic carcinogenesis and population studies. Despite the incomplete knowledge of fundamental biological and nutritional mechanisms that have an impact on cancer, there are enough research developments to justify an optimistic and aggressive approach to prevention-related research and practices. For this reason, the National Cancer Institute (NCI) has greatly increased its commitment to diet, nutrition, chemoprevention, and cancer research. This article presents an overview of the research potential of prevention initiatives, from basic research to clinical intervention trials. Advances in chemoprevention research, clinical intervention trials, and future prospects for cancer prevention, including biotechnology and the changing food supply, are also highlighted.

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## COLON CANCER

The NCI's comprehensive approach to cancer-prevention research, emphasizing life-style factors, provides opportunities to affect favorably the colon cancer rate and to address special attention to the disparities of incidence and mortality between whites and minorities. Colon cancer rates vary widely in different parts of the world, and these discrepancies may be attributed to dietary differences. The most recent incidence and mortality data from 1973 to 1988 indicate that colon cancer rates differ according to sex and racial groups. Since 1973, there has been an increase in the incidence of colon cancer in both whites and blacks, with the largest increase occurring in black males. The age-adjusted colon cancer incidence rates reported for whites by the NCI Surveillance, Epidemiology and End Results (SEER) program indicate a 5.4% increase from 1973 to 1988 and a 30.6% increase for blacks during the same period. For whites, the age-adjusted colon cancer mortality percentage change decreased 12.3% from 1973 to 1988; however, for blacks, the mortality percentage change for the same period increased 6.9% (*7*).

Several studies have also investigated the difference in colorectal cancer incidence and mortality rates for Puerto Ricans migrating to the United States. For Puerto Rican–born residents in New York City, incidence and mortality rates were twice those for Puerto Ricans living in Puerto Rico and one half to almost one third lower than other whites in New York City (*8*).

The association between diet and colon cancer was noted by Wynder and Shigematsu in 1967 (*9*) and by Burkitt in 1971 (*10*). These studies demonstrated that the lower intake of dietary fiber and higher intake of dietary fat in countries that are economically developed appear to play an important role in the increased risk of carcinogenesis in the Western world versus Africa. Many recent studies have examined the inverse relationship between dietary fiber and colon cancer. In 1990, Trock et al. (*11*) reviewed the epidemiological evidence and made an aggregate assessment of the strength of the evidence of a relationship between fiber and cancer. Thirty-one of 43 studies assessed showed strong or moderate support for a cancer hypothesis involving fat and fiber intake.

Both epidemiological and animal studies link dietary fat to colon cancer. In 1988, Graham et al. (*12*) found a significant positive association of fat intake with colon cancer when 428 colon cancer patients, classified by quartile of fat intake, were compared with matched control subjects. In 1990, Willett et al. (*13*) found that the relative risk of colon cancer was 2.49 for women who ate animal fat (eg, from beef, pork, or lamb) every day, whereas the consumption of fish and chicken without the skin was associated with decreased risk.

Vogelstein et al. (*14*) found a genetic component for colon cancer susceptibility combined with acquired changes in cell genetics later in life. When studying genetic damage in colon epithelium in patients with colon polyps, they found that, as the severity of colon polyp disease increased, the number of genetically damaged cells increased. The identification of a specific gene localization for adenomatous polyps may lead to premalignancy diagnosis at various stages of carcinogenesis and may provide new leads for effective interventions. The implication of these findings is the importance of genetic elements in this multistep process. Studies such as this are important research opportunities for intervention before the onset of malignancy.

Advances in molecular biology, carcinogenesis, and epidemiology have facilitated the bridge to applied research, including human trials related to cancer prevention. The clinical trial research on colon carcinogenesis has been particularly noteworthy over the past several years. In 1988, DeCosse et al. (*15*) completed a double-blind placebo-controlled clinical trial of dietary wheat bran fiber plus vitamin C and E supplements to prevent polyp recurrence in 72 patients with familial polyposis. Trial results indicated that, although no effect was observed for the vitamin supplements, there were fewer adenomatous colon polyps in patients whose intake of wheat bran fiber was in excess of 11 g/day.

There is also increasing interest in studies with intermediate end-point markers in clinical trial research. For colon cancer, clinical and biochemical markers currently under assessment include intermediate end points measuring the multiplicity of new colon adenomas, prostaglandin synthetase, ornithine decarboxylase mucosal monitoring, and [$^3$H]thymidine labeling index determinations of epithelial cell proliferations. In a 1989 study by Lipkin et al. (*16*), supplemental dietary calcium decreased hyperproliferation in epithelial cells of subjects at increased risk for familial colon cancer.

## BREAST CANCER

The increase in breast cancer incidence from 84.8/100 000 in 1980 to 112.5/100 000 in 1987 may reflect an unfavorable dietary influence on breast cancer risk (*7*). Women in countries with the lowest to highest percentage of calories from fat vary fivefold in breast cancer incidence rates (*17*). Dietary fat consistently is observed to promote tumors in experimental studies. In a review of 100 animal studies involving 7838 rats and mice comparing the effects of different levels of dietary fat and/or calorie intake on breast tumor development, both higher fat intake and higher calorie intake independently increased breast tumor incidence (*18*).

Menopause, obesity, and possibly a high-fat Western-type diet may influence estrogenic serum levels and increase breast cancer risk (*19*). In 1990, Prentice et al. (*20*) found that concentrations of total and weakly bound plasma estradiol were significantly reduced in 73 healthy postmenopausal women after 10–22 weeks of participation in a dietary intervention trial aimed at reducing fat intake to 20% of calories. In a study of 27 postmenopausal women, plasma androgens and sex hormone–binding globulin were higher in the omnivorous versus the vegetarian women. Breast cancer patients had the highest hormone levels, indicating that this hormonal pattern may be associated with a high-fat diet and is accentuated in women with breast cancer (*21*).

In 1979, Hopkins and Carroll (*22*) observed a strong positive correlation between the intake of dietary fat and breast cancer mortality in 39 countries. The range in breast cancer incidence rates in 21 countries strongly correlates with national estimates of per-capita fat intake (*17*).

Migration data among women from areas with lower breast cancer rates to areas with higher rates show increased breast cancer risk. This trend is seen among Japanese women migrating to Hawaii (*23*) and Italian women migrating to Australia (*24*). A study of Polish immigrants to the United States reported considerably higher cancer rates for the immigrants than for Polish citizens (*25*).

Results from case-control studies evaluating the relationship between dietary fat and cancer have been inconsistent. Combined analyses of 12 case-control studies showed a positive association of saturated fat intake with breast cancer in postmenopausal women (*26*). In 1987, however, Willett et al. (*27*) analyzed self-administered questionnaires from a cohort of 89 538 nurses and found no difference in breast cancer incidence between the lowest and highest quartiles of fat intake. A possible explanation for this disparity is the measurement error in dietary ascertainment, which introduces a bias toward the null in epidemiological case-control and cohort studies.

In a study that examined the prevention of contralateral breast cancer, Fisher et al. (*28*) found that in 1400 patients treated with the antiestrogen tamoxifen, only 23 new cancers developed in the treated group while 41 second primary cancers occurred in the control group. These data, along with other benefits reported with tamoxifen use in adjuvant therapy for breast cancer, have prompted proposals to further test the chemopreventive effects of this drug (*29*). Beginning with a feasibility pilot study to determine the efficacy of tamoxifen in postmenopausal women, a chemoprevention trial is being implemented by the NCI and the National Heart, Lung, and Blood Institute. The full trial will enroll 16 000 women for 7 years using the NCI Community Clinical Oncology Program Network. The primary aim is to assess the impact of tamoxifen on

the development of breast cancer in high-risk women, to evaluate the effects of tamoxifen on coronary heart disease, and to evaluate the agent's effect on osteoporosis. For the Tamoxifen Chemoprevention Trial, an initial cardiovascular profile and electrocardiogram will be obtained for each subject. Baseline and intermediate measures of serum lipids will also be performed.

## PROGRESS IN CHEMOPREVENTION

The long interval of two to three decades between the first carcinogenic exposure and the appearance of a malignancy provides an opportunity for chemoprevention in modifying the progression of the disease from a precancerous condition to invasive cancer. In 1982, the NCI Chemoprevention Program was established to identify and characterize new agents with proven efficacy in preventing carcinogenesis in animal models and a high probability of preventing cancer in humans, to conduct preclinical efficacy and toxicity testing of candidate agents, and to conduct clinical prevention trials with efficacious and safe agents that potentially may suppress tumorigenesis in humans. To accomplish this agenda, the NCI Chemoprevention Program has developed a system for identifying and testing the promising agents shown in figure 1. Conducted in stages, the NCI Chemoprevention Program screens potentially useful compounds in a preclinical setting followed by the selection of promising candidate inhibitors in human intervention. Approximately 800 agents are under consideration for development, with more than 100 agents or combinations of agents undergoing preclinical evaluation.

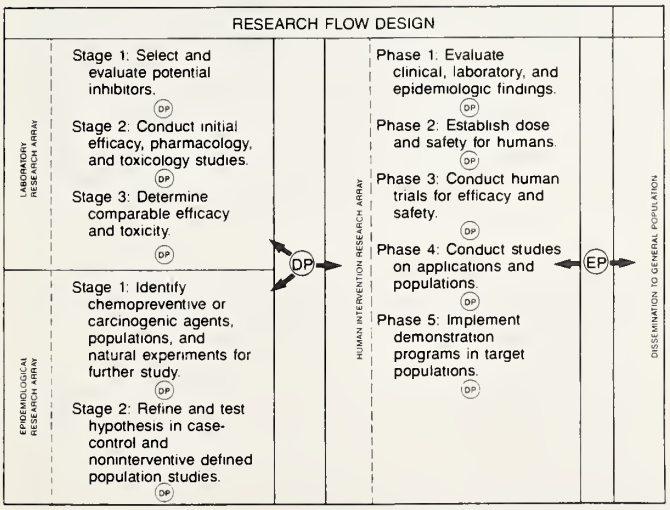


**Figure 1.**—National Cancer Institute chemoprevention program. DP, decision point; EP, evaluation point.

Reduced tumor incidence has been demonstrated in animal systems using pharmacological amounts of vitamins C, E, A, and related analogues; calcium; β-carotene; and other carotenoids (*30*). A broad spectrum of anticancer plant constituents is of interest to the chemoprevention program. The NCI is currently identifying cancer-inhibiting factors in soybeans. Studies in animal models have identified five classes of anticarcinogenic compounds in soybeans: isoflavones, protease inhibitors, phytosterols, saponins, and inositol. Because of the anticancer activity of soybeans demonstrated in preclinical experiments and the lower breast and colon cancer rates in countries that consume large amounts of soybean products (eg, Japan and China), participants at an NCI-sponsored workshop recently recommended further studies on the cancer-preventing potential of soybean components and products.

The feasibility of clinically assessing the efficacy and safety of chemopreventive agents has been established. More than 40 human chemoprevention trials sponsored by NCI are in progress, mostly in high-risk populations and in medical settings. The success of this program is shown in the results from several clinical studies. For example, in 1986, Hong et al. (*31*) demonstrated temporary remission of oral leukoplakia and reversal of oral dysplasia with 13-*cis*-retinoic acid, indicating the potential of this retinoid in preventing oral cancer in a high-risk population. The patients in this study had an initial positive response of 67% in the treated group and only 10% in the placebo group. A more recent clinical chemoprevention trial by Hong et al. (*32*) found that 13-*cis*-isotretinoin prevented the occurrence of second primary head and neck tumors in patients at high risk for the recurrence of these malignancies. Prospectively studied were 103 randomized patients who were free of disease after primary treatment for squamous-cell cancers of the larynx, pharynx, or oral cavity with 50–100 mg isotretinoin • $m^{-2}$ body surface • $d^{-1}$ or placebo for 12 months. Results indicate that daily treatment with high doses of isotretinoin is effective in preventing second primary tumors in patients previously treated for squamous-cell head and neck cancer, although isotretinoin did not affect the recurrence rate of the initial cancer.

NCI and the National Public Health Institute of Finland are conducting a large-scale lung cancer-prevention trial testing the oral administration of β-carotene and α-tocopherol in a population of heavy smokers (*33*). With a lung cancer incidence among the highest in the world coupled with marginal per-capita intake of several micronutrients, Finland offers a unique environment for the study of lung cancer prevention. Four separate treatment groups are being evaluated in a population of 29 000 men, aged 50–69 years, with a 2 × 2 factorial design. The use of factorial designs, which evaluate two or more hypotheses in a single trial with a minimal increase in cost, is particularly suited to prevention trials (*34*).

Of the many other cancer prevention trials in progress, 11 are examining the effects of β-carotene, alone or in combination with other agents, on cancer incidence. For

example, a trial conducted by Hennekens (*35*) is under way with 22 000 healthy male physicians, aged 40–84 years, to evaluate the influence of β-carotene and aspirin on both total cancer incidence and cardiovascular disease, with a factorial design. The aspirin arm of the study has been completed, and results from the β-carotene arm are expected in the near term.

## BIOTECHNOLOGY AND CHANGES IN FOOD SUPPLY

In the public health arena, it is important to understand what has led to the major changes over the century in disease frequency. Why has stomach cancer dropped off so dramatically in the United States? This is probably due to improvements in the food supply, ie, better means of avoiding contamination and year-round availability of vegetables and fruits. A major emphasis on diet and cancer and on chemoprevention research might bring about the same favorable change over the next several decades with respect to cancers of the breast, colon, prostate, and others.

New technologies may reduce cancer risk because of their potential to change the nutrient or chemical constituents of foods. For example, of all the dietary component studies, fat intake offers the strongest evidence for a causal relationship with cancers of the breast, colon, and prostate. The food industry, driven by consumer demand, has taken steps to incorporate existing knowledge concerning diet and disease in the development of new lower-fat or fat-free products. In addition, sharp reductions are being made in the total fat content of beef and pork through breeding, genetic improvement, and the use of growth hormones (eg, somatotropin).

Advances in product development have also been used to increase the availability and variety of vegetables and fruits and other fiber- and nutrient-rich foods. Many studies have reported that daily consumption of vegetables and fruits is associated with decreased incidence of lung, bladder, esophageal, and stomach cancers. Development of new or improved food ingredients through genetic engineering has led to the enhancement of characteristics, eg, taste, shelf life, or nutritive quality. For example, new germination techniques can produce a 10-fold increase in the vitamin C content of peas and beans. The knowledge gained by investigators studying the regulation of ripening enzymes also will lead to the availability of tomatoes that taste vine ripened yet do not soften before reaching the market (*36*). This trend toward improving vegetables and fruits is favorable because, in addition to their beneficial nutritive and nonnutritive constituents, these foods have value in displacing high-fat foods in the diet.

Developments in biotechnology may lead to consumption of the recommended diet with lower fat, lower calories, higher fiber, and increased amounts of vegetables and fruits. However, an intensive research program is needed to specify the type and amount of cancer-preventive components these products should include to reduce cancer risk. Although industry is progressing rapidly with biotechnology developments, the implications of these products for health promotion and disease prevention must be clearly understood.

NCI has initiated a new approach to cancer-prevention research, the "designer-food project." Now in the developmental stage, the project is a multidisciplinary initiative involving food science and technology, analytic methodology, biotechnology, clinical metabolism, and dietary interventions in both healthy subjects and people at high risk for cancer. This project aims to increase our understanding of the relationship between plant foods in the diet and to show how the composition of foods and food products can best be modified to contribute to lower cancer risk.

## FUTURE PROSPECTS

In the medical area, it is my view that the scope of oncology practice and perhaps the scope of medical practice will change. Oncology and medicine of the future will be broadened to include much greater attention to aspects of prevention. Diet and cancer and chemoprevention research will continue to be major programs at NCI. These research areas provide the opportunity for building on detailed descriptions of the critical events of the carcinogenic process and for testing interventions in clinical trials aimed at the prevention of human cancers. The goal of these programs is to narrow the window of time between predicting cancer risk and implementing prevention strategies.

Future areas of emphasis related to cancer prevention are outlined in table 1. NCI will emphasize public guidance about smoking, diet, and other aspects of prevention as research advances. Clinical trials in prevention will be of increasing importance as will the translation of basic research to clinical studies and the translation of the results of these studies into public applications. Study protocols incorporating biomarkers require fewer resources (time and number of subjects) and may be statistically more precise than standard prevention trial designs with cancer as the end point. Advances in genetic and molecular biology may allow asymptomatic individuals at risk for common cancers (eg, of the colon) to benefit from interventions aimed at preventing progression to malignancy.

**Table 1.**—Future prospects for cancer-prevention research

| |
|---|
| Public guidance as research continues |
| Smoke-free society |
| Dietary guidance |
| Cancer-prevention trials |
| Medical setting |
| Public health setting |
| Biomarkers |
| Biotechnology changes in food supply |
| Sensitivity to environment |
| Cancer prevention in mainstream of major research institutions |

With all of the information available to the public concerning cancer prevention and the emergence of new products from advances in biotechnology, guidance is necessary to ensure the best application of these recommendations and products. Working to refine dietary recommendations should not preclude the dissemination of existing health information to the public. This parallel knowledge is needed in the areas of chemoprevention and clinical prevention trials. In addition, cancer-prevention research must be built into the mainstream of cancer research conducted at universities and cancer centers to have an even greater impact on reducing cancer incidence.

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# Evidence and Overview of Global Tobacco Problem

Nigel Gray[1]

**ABSTRACT—Tobacco use, both smoking and chewing, is a very old habit. Machine-made cigarettes appeared early in this century. As a consequence, lung cancer increased substantially. The evidence relating cancer to smoking and chewing is summarized. Various forms of tobacco use are briefly described. Tobacco exports are an important source of hard currency for some developing countries. In the Western world, seven major international companies control major market shares. In contrast, tobacco monopolies exist in eastern Europe, Japan, and China. The public health interests are represented by the relevant national and international associations and some governments. Smoking is the largest cause of avoidable death in developing countries after infectious disease and malnutrition. [J Natl Cancer Inst Monogr 12:15–16, 1992]**

Hookah smoking has been present for many centuries in the East. Medical textbooks of the last century reflect associations between pipe smoking and other forms of tobacco use and diseases of the mouth. The arrival of the machine-made cigarette in the early part of this century set the stage for an upsurge in cigarette smoking that continued in developed countries until the 1980s. In 1950, evidence appeared incriminating cigarettes as a cause of lung cancer and later heart disease.

The form of evidence available is simple and well known (*1*). There is a dose-response relationship between the number of cigarettes smoked and risk of lung cancer—more smoking equals more lung cancer risk. The same relationship exists between duration of smoking and risk of lung cancer—longer smoking history equals larger risk of lung cancer. Depth of inhalation increases the risk of lung cancer.

The encouraging information is that the relative risk of lung cancer decreases progressively when smoking ceases, albeit slowly. Heart disease risk decreases even more rapidly.

There is no question that cigarette smoking is one of the largest causes of avoidable disease in the world today. It ranks behind infectious disease and malnutrition as a cause of mortality in developing countries, whereas it is the premier cause of avoidable death in developed countries.

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## FORMS OF SMOKING AND TOBACCO USE

Forms of tobacco use are as diverse as they are widespread. The hookah has been used throughout the East and in India for centuries. It is frequently known as the "hubble bubble" and includes a water bath attached to two long tubes that put about 3 feet of air between the source of tobacco and the smoker. It is associated with chronic bronchitis and (because it is a group activity) is the probable cause of some spread of tuberculosis. No known association exists with lung cancer, perhaps because the dose of tar delivered is relatively small.

The manufactured cigarette represents the most widespread form of tobacco use in developed countries and in parts of the developing world with enormous populations, including the USSR and China. Cigarettes in sophisticated countries contain 15 mg of tar and 1 mg or less of nicotine. Cigarettes in the USSR, China, other developing countries, and Indonesia frequently exceed 30 mg of tar. The highest-tar cigarette so far discovered is the Indonesian kretek, with 60 mg.

In India, there are many forms of tobacco use. The cheroot is a thick, tightly rolled tube of tobacco that yields an extremely strong smoke that is generally not inhaled, is held in the mouth, and is associated with cancer of the head and neck. Reverse smoking is a process whereby a small cheroot is held with the lighted end inside the mouth to conceal the fact that the user is smoking. The result is cancer of the palate and other parts of the mouth. Bidi smoking is widespread in India. This is a slender rolled tube of tobacco delivering a tar content between 25 and 30 mg. Cigarettes are also widely used in India, and the location of disease attributable to cigarettes and other products depends on the form of tobacco smoked. Chewing of betel nut together with tobacco and lime occurs throughout India and Southeast Asia. It is responsible for many cancers of the head and neck.

Tobacco use of one form or another is responsible for one third of all cancer seen on the Indian continent. Tobacco is widely used in Papua New Guinea, both as cigarettes and as twisted black tobacco wrapped in newspaper in long tubes known as brus. Betel nut is commonly chewed throughout Papua New Guinea, the Solomon Islands, and Vanuatu but not in New Caledonia. Betel is chewed in these countries without the addition of tobacco. Anecdotally, it leads to considerable leukoplakia and some cancer of the mouth.

Evidence from India incriminating the various forms of tobacco use in head and neck and lung cancer is of similar form to that of the major Western studies (*2*). Dose re-

sponse is clear, and site of cancer caused relates logically to the way in which tobacco is used and the tissue most exposed. Fine-cut snuff chewing is common in Indonesia, another habit associated with cancer of the mouth.

## WORLD TOBACCO PRODUCTION

Some of the largest producers and users of tobacco are developing countries. China produces 2 million metric tons of tobacco, most of which is used in China. US production is substantial, and whereas US production was almost equivalent to US use in 1980, US production exceeded use by at least 30% by 1988 (*3*). The remainder went into export. Europe is a net importer of tobacco, importing approximately as much as it uses. Africa is a net exporter, exporting approximately twice as much as it uses.

In summary, tobacco is an important earner of hard currency for developing countries, but it is also an important earner of hard currency for wealthy countries such as the United States and United Kingdom.

## INTEREST GROUPS INVOLVED

The number of interests in the worldwide marketing of tobacco is relatively small. The seven major international tobacco companies are centered in the United Kingdom and the United States. Tobacco monopolies exist in the USSR, many other eastern European countries, Austria, France, Japan, and China. Some of these monopolies have recently been taken over by US companies.

In opposition to the interests of the tobacco industry are those of international public health organizations. The World Health Organization (WHO) is the major governmental agency involved. Nongovernment agencies such as the International Union Against Cancer, International Union Against Tuberculosis and Lung Disease, International Organisation of Consumer Unions, International Society and Federation of Cardiology, and others complement WHO activity with political and activist support.

The results of the battle between those who want to expand markets for tobacco and those who want to shrink them have been simple and clear. Over the past two decades, tobacco consumption has started to fall in developed countries whereas it has started to rise in developing countries. The machine-made cigarette is replacing many indigenous forms of tobacco use, and as the epidemic of head and neck cancer is reduced by early detection and better treatment, as well as education of the developing countries, lung cancer driven by international advertising will probably replace it. It is therefore important that we start work now. Table 1 lists the diseases attributable to tobacco (*1*).

**Table 1.**—Diseases attributable to tobacco

| |
|---|
| Causal |
| Cancers of lung, larynx, mouth, and esophagus |
| Chronic bronchitis |
| Coronary heart disease |
| Peripheral vascular disease |
| Chronic obstructive pulmonary disease |
| Intrauterine growth retardation |
| Low-birth-weight babies |
| Stroke |
| Probable cause |
| Unsuccessful pregnancy |
| Increased infant mortality |
| Peptic ulcer |
| Contributing factor |
| Cancers of bladder, pancreas, kidney, and cervix |

Adapted from (*1*).

In summary, tobacco will be responsible for at least 3 million deaths per year during the 1990s (*4*), and this number is expected to increase progressively and steeply over the next two to three decades. Of lifetime smokers, at least 25% will die because they smoke. Smokers lose, on average, 20 years of life if they suffer their smoking-associated death in middle age (35–69 years), when most of these deaths occur.

Smoking is the largest cause of avoidable death in developed countries and ranks third behind infectious diseases and malnutrition in developing countries. In certain developing countries such as China and the USSR, where cigarette smoking has been widespread for many decades, tobacco use will probably soon be the major cause of death.

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# Positive Evidence on Effectiveness of Selected Smoking Prevention Programs in the United States

David M. Burns[1]

**ABSTRACT—Various smoking intervention approaches have been demonstrated to successfully alter smoking behavior among individual smokers, but it is difficult to demonstrate the benefit of these individual cessation approaches across the population of smokers. In contrast, efforts that concentrate on altering the social and economic environment within which the smoker smokes, most notably the media, taxation, and changing the social acceptability of smoking, have been linked to substantial shifts in the smoking behavior of the US population. Attacking tobacco use as a form of sociological carcinogenesis, rather than focusing on the individual smoker, allows alteration at the root of smoking behavior, ie, its personal, social, and psychological utility for the smoker. [J Natl Cancer Inst Monogr 12:17–20, 1992]**

Much of the discussion in this conference dealt with chemical and environmental carcinogenesis and the prevention of cancers by alterations in individual behavior or in the immediate environment within which the individual lives and works. This perspective is perhaps too narrow to encompass effective tobacco control strategies. Perhaps the most appropriate view of tobacco-related cancers is one of sociological carcinogenesis. The forces that led to the development of widespread cigarette use in this century, the forces that currently lead to initiation of smoking among adolescents, and the forces driving smoking cessation can be viewed as social and economic forces leading to the development or prevention of cancer. The tobacco manufacturers become the "vector" and cigarette smoking becomes merely the mechanism by which these social and economic forces produce cancer. This view shifts the concentration of tobacco control efforts from the individual smoker to the environment that promotes and condones smoking. The personal psychological and sociological utility of cigarette smoking is the essence of the hold that the cigarette has on the smoker; to remove this hold, the social environment within which the smoker lives must be altered to provide persistent and inescapable messages to quit.

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## FORCES INFLUENCING TOBACCO USE IN THIS CENTURY

Figure 1 presents US per-capita consumption of cigarettes from 1900 until now. Per-capita consumption is the number of cigarettes sold divided by the population over age 18 years. Cigarette smoking in the United States, in contrast to other forms of tobacco use, has been largely a twentieth century phenomenon rising from 54 in 1900 to a peak of over 4300 in 1963. The first major upsurge in cigarette consumption occurred during the First World War, when many men were mobilized into military service and, as part of the socialization process of entering military service, learned to smoke. There was a brief downturn in per-capita consumption during the Depression, demonstrating that cigarette smoking is influenced by the availability of disposable income and the cost of cigarettes. There was an enormous increase in cigarette use during the Second World War, again reflecting the mobilization of men into military service, with the tobacco companies having learned from giving away free cigarettes to the troops in the First World War. Equally important in regard to this upsurge of per-capita consumption, however, was the movement of many women from the home into the work force. With this movement came increased social autonomy and income, and women began to smoke cigarettes in large numbers.

Of more interest are the downturns in per-capita consumption that have occurred since 1950. The first of these was in 1954 and coincided with the publication of data on the disease risks associated with smoking. The second downturn occurred between 1967 and 1970, when, under the Fairness Doctrine, the Federal Communications Commission required television stations to run antismoking spots to balance the cigarette commercials then being aired on television. Many antismoking spots with both health and other themes were aired, and the per-capita consumption fell. In 1970, tobacco advertising on television was banned, antismoking spots effectively disappeared, and per-capita consumption rose. Beginning in 1974, percapita consumption once again decreased and has continued to do so. This trend has been attributed to the movement for nonsmokers' rights and to developing the social unacceptability of smoking. The downturn in per-capita consumption accelerated perceptibly with the increase in the federal excise tax in the early 1980s.

The responsiveness of a coarse measure of cigarette use, eg, per-capita consumption, to these social changes dem-

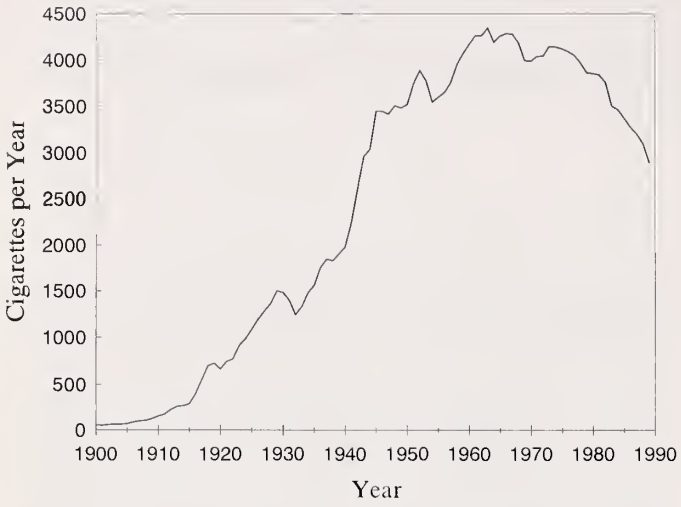


**Figure 1.**—US per-capita consumption of cigarettes from 1900 to 1990 among individuals over age 18 years.

onstrates the potential for larger social and economic changes to influence smoking behavior. I present data on two of these changes, ie, public information and media campaigns and increasing the cost of cigarette use.

## PUBLIC INFORMATION AND MEDIA CAMPAIGNS

To understand the response of smokers to the public information and media efforts that have been made in the United States, it is necessary to describe the pattern of changing smoking behavior with age. Figure 2 shows the prevalence of current and ever smokers for a cohort of men born in 1911–1920. The initiation of regular smoking is essentially complete by age 25–30 years, and few individuals take up smoking after that age. Cessation is the major smoking behavior change occurring after age 30 years.

The prevalence of current smoking for successive birth cohorts of black and white men demonstrates that the general pattern of uptake early in life with cessation later in life is true for all birth cohorts, with differences in age of initiation and peak smoking prevalence among the cohorts (fig. 3). This problem suggests that cessation may be largely a function of the age of the smoker. However, when the fraction of former smokers in each of the four oldest birth cohorts of black and white men is plotted by calendar year, there is only a small effect of age, with most of the change to former smoking status being a function of the calendar year (fig. 4). This link to calendar year is even more evident when the 5-year quit rates for the three oldest birth cohorts of black and white men are

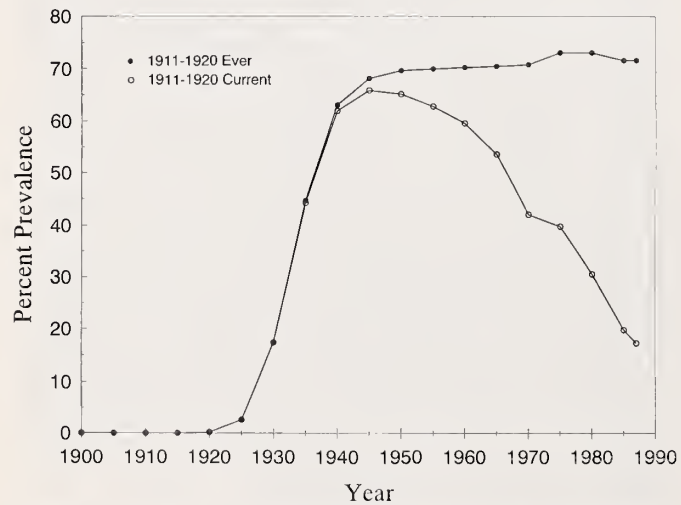


**Figure 2.**—Prevalence of cigarette smoking among US men born between 1911 and 1920.

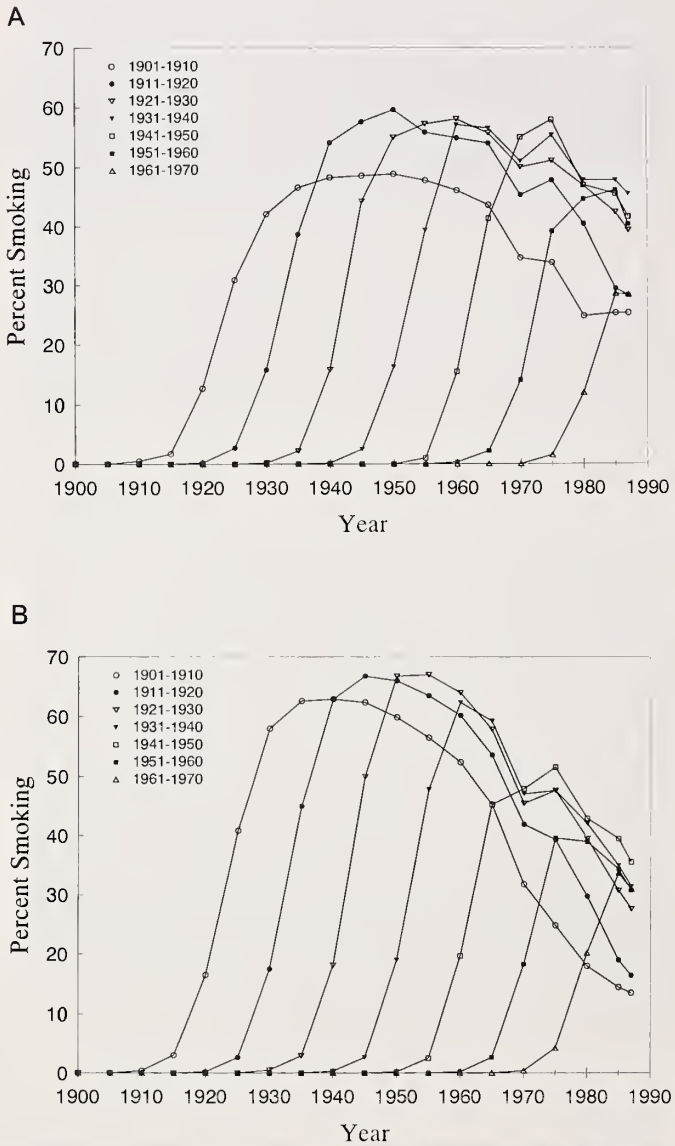


**Figure 3.**—Change in prevalence of cigarette smoking among successive birth cohorts of black (A) and white (B) US men, 1901–1970.

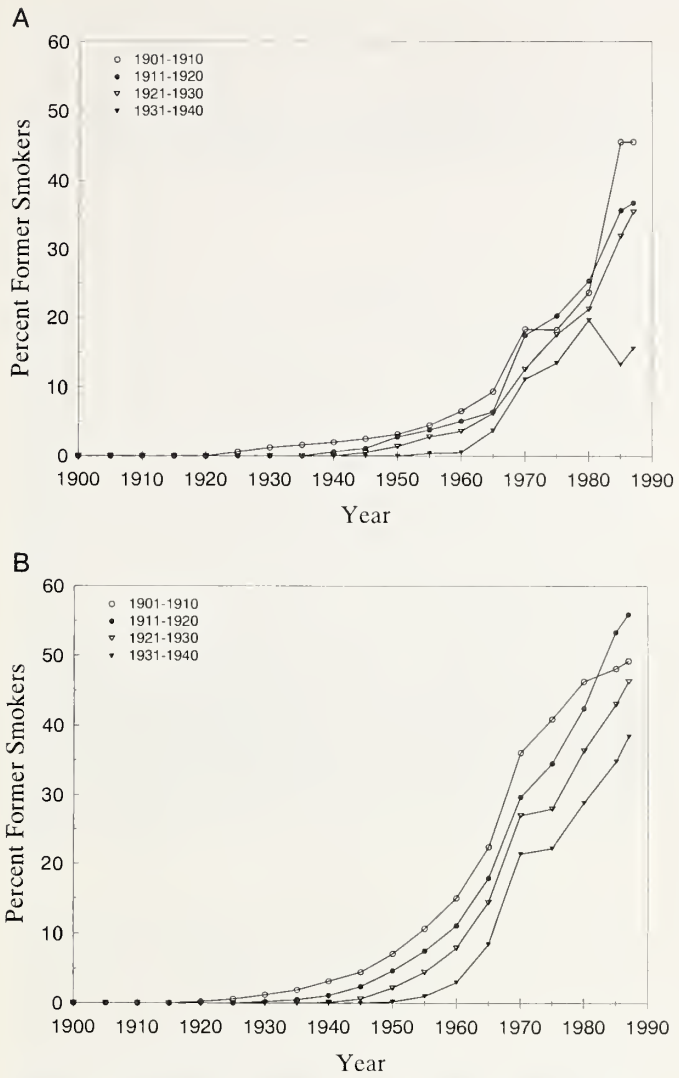


**Figure 4.**—Change in prevalence of former smokers among successive birth cohorts of black (A) and white (B) US men, 1901–1940.


**Figure 5.**—Five-year interval change in prevalence of former smokers among successive birth cohorts of black (A) and white (B) US men, 1901–1930.

plotted (fig. 5). These cohorts were chosen because they would have reached age 25 years by the mid-1950s, when the first decrease in per-capita consumption occurred; the change in the percentage of former smokers for each 5-year period is plotted for each cohort. Again, the predominant relationship is clearly with calendar year rather than age, but there is a minor difference between the responses of black and white men; for white men, there is little cessation activity before 1950 but a clear and increasing rate of cessation after 1950. This cessation activity coincided with the early public information campaigns in the print media warning of the health risks. Between 1965 and 1970, there was a dramatic increase in the conversion of smokers to former smokers, coinciding with the antismoking spots on television to counterbalance the cigarette commercials. The cessation pattern for black men also showed a dramatic change at the time of the antismoking spots, but there was a virtual absence of cessation among black men during the public information effort that preceded the television campaign.

Although it is attractive to attribute the absence of cessation activity among black men to differences in socioeconomic states between black and white populations, the same lack of cessation activity before the television antismoking campaign was demonstrated for the oldest cohorts of white women. Early health-risk data, obtained largely on white men, did not result in blacks and white women receiving the health message. However, the television campaign, which used both health and other messages, was able to reach and promote cessation across racial and sex lines.

## TAXATION

Increasing the cost of cigarettes has been one of the major interventions suggested to alter smoking behavior. Beginning in January 1989, the tax on cigarettes was increased by 25 cents/pack in California. Measures of

smoking prevalence show a decline of over 5% (from 26% to 21%) between 1986 and 1990. Data on the sale of cigarettes in California suggest that a substantial fraction of the change in prevalence occurred around the time of the tax increase. Figure 6 shows the sale of cigarettes in California as a 12-month running average; there was a clear acceleration in the rate of decline that occurred at the time of the tax increase. The figure contrasts the per-capita sales in California with those of the rest of the United States to show that the acceleration in the decline present in California was not part of a national trend. Clearly, a major change in smoking behavior occurred in California with the passage of the excise tax. It remains to be seen whether the programs that are being funded by the tax will be able to sustain this increased rate of decline.

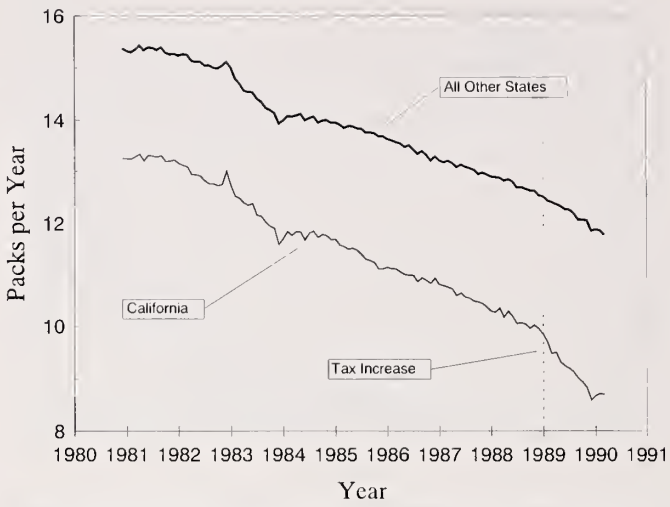


**Figure 6.**—Per-capita consumption of cigarettes from 1981 to 1990 for California and all other states.

## SUMMARY

Current tobacco-control strategies are directed at altering the environment within which a smoker lives and smokes. This approach provides persistent and inescapable messages to the smoker to quit and reduces the personal and social utility of smoking for the smoker. Changes in smoking prevalence are associated with changes in the level of taxation and with national media campaigns directed at smoking. The shift in tobacco-control strategies from a focus on the individual to a focus on the environmental influences that promote cessation is likely to lead to continued, and perhaps accelerating, reductions in the prevalence of tobacco use.

# Trends in Tobacco Use in Europe

Catherine Hill[1]

**ABSTRACT—Tobacco consumption in Europe can be estimated from several sources, including sales statistics and population surveys. The first source provides a reasonable estimate of total tobacco consumption, whereas the second gives estimates of the prevalence of smokers by sex and age. In 1950, daily cigarette consumption by adults in European countries varied between 1.7 in Portugal and 6.9 in Ireland, the corresponding US consumption being 8.9. In 1989, the variation was much smaller, ie, between 3.5 in the Netherlands and 10.1 in Greece. In the countries where consumption was high in 1950, maximum consumption was achieved around 1975, followed by stabilization or reduction. In other countries, where consumption was low in 1950, it is still increasing. In a 1987 European survey, the proportion of current smokers varied between 33% in Portugal and 46% in Denmark. Much of this difference comes from the low prevalence of smoking habits in the adult female population of southern Europe. [J Natl Cancer Inst Monogr 12:21–24, 1992]**

Whenever US health professionals visit the largest cancer hospital in France, Institut Gustave Roussy, they are horrified by the number of smokers among the staff. The same impression can be obtained in many other countries of Europe, particularly southern Europe. It is therefore tempting to infer that total tobacco consumption is higher in France, or in Europe, than in the United States; however, this inference is not correct. I present data on tobacco smoking in the countries of the European Economic Community (EEC) and compare them with data on the consumption in the United States.

## METHODS

All data on tobacco and cigarette consumption until 1973 were derived from Lee (*1*), except for the data on cigarette consumption for Spain (*2*). After 1973, the sources were Ferraroni et al. (*3*) and Mastrandrea (*4*) for Italy, Vioque and Bolumar (*2*) for Spain, Wald et al. (*5*) for the United Kingdom, Warner (*6*) for the United States, and documents from the EEC and the World Health Organization (*7–9*). Information on the prevalence of smoking in EEC countries comes from the 1987 European survey (*10*) and in the United States from *Morbidity and Mortality Weekly Report* (*11*).

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## RESULTS

Table 1 gives the sales of manufactured cigarettes per adult (age $\geq$15 years) and per day for EEC countries and the United States. In 1950, the daily cigarette consumption per adult in EEC countries varied from 1.7 in Portugal and the Federal Republic of Germany (FRG) to 6.9 in Ireland, which was well below the 8.9 cigarettes consumed daily in the United States at that time. Ireland and the United Kingdom were the only European countries where at least 6 cigarettes/day were consumed, and the consumption was less than 4 cigarettes in most other countries and less than 2 in Spain, Portugal, and FRG. Figure 1 illustrates the consumption of manufactured cigarettes in European countries.

Compared with 1950, the consumption was higher in 1989 everywhere except in the United Kingdom and varied between 3.5 in the Netherlands and 10.1 in Greece. Figure 2 shows the consumption of cigarettes in 1988, which is the last year for which data are available for all the European countries. Cigarette consumption was particularly high in Greece, Switzerland, Yugoslavia, Hungary, and Poland.

The trends were different among countries. Table 1 gives the maximum consumption and year in which it was observed for each country of the EEC and for the United States. Figure 3 illustrates the detailed trends for the United States, the United Kingdom, and France. The United States, the United Kingdom, and Ireland (for which data are not shown, but see table 1) have the largest past exposure to manufactured cigarettes. They are also the countries that have been most successful in reducing consumption. In other countries, the consumption increased rapidly until 1975, after which the trend moved upward more slowly, stabilized, or even moved downward.

In 1985, cigarettes represented a proportion of the total tobacco consumption, which varied from 61% in the Netherlands (where hand-rolled cigarettes are common), and 64% in Denmark (where pipe smoking is common) to 100% in Greece (table 2). The proportion of tobacco represented by manufactured cigarettes was much smaller in 1950, when it represented as little as 35% of tobacco sales in several countries.

Sales statistics provide good information on total tobacco consumption, but surveys are needed to describe the population of smokers. In a 1987 European survey, the fraction of the population reporting never having smoked varied from 34% in the Netherlands to 56% in Portugal (table 3). The proportion of ex-smokers was highest in the

**Table 1.**—Sales of manufactured cigarettes per adult (age ≥15 years) units/day

| Country | 1950* | 1970* | 1989† | Maximum (year) |
|---|---|---|---|---|
| Belgium | 3.4 | 6.5 | 5.0 | 7.5 (1973) |
| Denmark | 3.5 | 4.6 | 5.2 | 6.4 (1976) |
| France | 2.5 | 5.0 | 5.7 | 6.0 (1985) |
| FRG | 1.7 | 6.9 | 6.4 | 7.3 (1975) |
| Greece | 4.4 | 6.2 | 10.1 | 10.2 (1987) |
| Ireland | 6.9 | 8.2 | 7.3 | 9.7 (1974) |
| Italy | 2.2 | 4.7 | 5.8 | 6.8 (1985) |
| Netherlands | 3.1 | 5.4 | 3.5 | 8.4 (1977) |
| Portugal | 1.7 | 3.8 | 5.2 | 5.5 (1987) |
| Spain‡ | 1.8 | 5.9 | 6.7 | 7.4 (1987) |
| United Kingdom | 6.0 | 8.4 | 5.5 | 8.8 (1973) |
| United States | 8.9 | 10.0 | 8.0§ | 10.7 (1963) |

*From (*1*).
†From (*7*) for consumption data and (*8*) for population data.
‡From (*1*) and Vioque J: unpublished observations.
§For 1987 and from (*6*).


**Figure 1.**—Daily cigarette consumption per adult, Europe, 1950. NA, not available. Data from (*1*).

United Kingdom, where it reached 24%. The proportion of current smokers varied from 33% in Italy, Ireland, and Portugal to 46% in Denmark and 44% in the Netherlands. The difference in smoking habits between men and women was significant in southern Europe (table 4): the proportion of smokers among men was more than twice that among women in Portugal, Greece, and Spain. This difference was largest in the older age groups and disappeared in the population aged 15–24 years (data not shown).

Social class and/or education are important determinants of smoking status in most countries, but their effects are not uniform. This is illustrated with data from Italy (*11*) and the United Kingdom (*5*). Figure 4 shows that the proportion of smokers is smallest in social classes I and II (the wealthiest) among both men and women in the United Kingdom. In contrast, in Italy, higher education coincides with fewer smokers among men but more among women.

EEC countries not only have diverse smoking habits, but they also have different attitudes toward the economic and regulatory aspects of the problem. This is illustrated by the variation in the cost of the most common cigarette

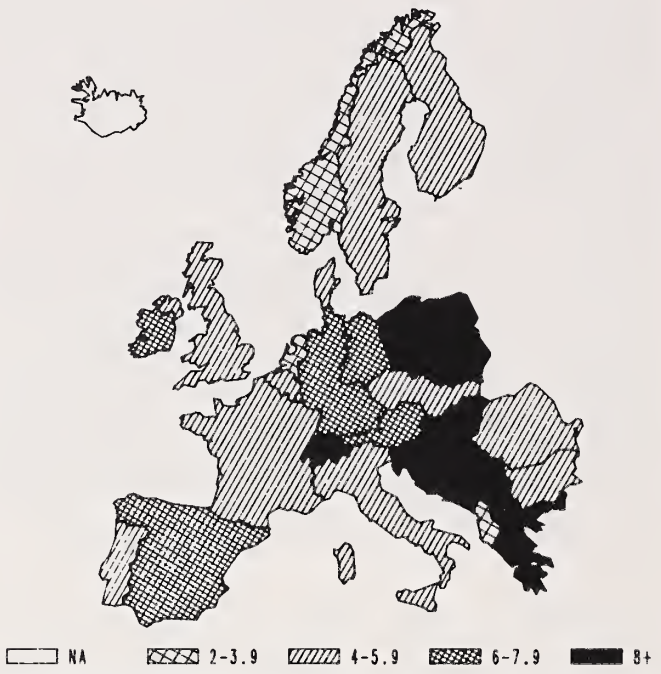


**Figure 2.**—Daily cigarette consumption in Europe, 1988. NA, not available. Data from (*12*).

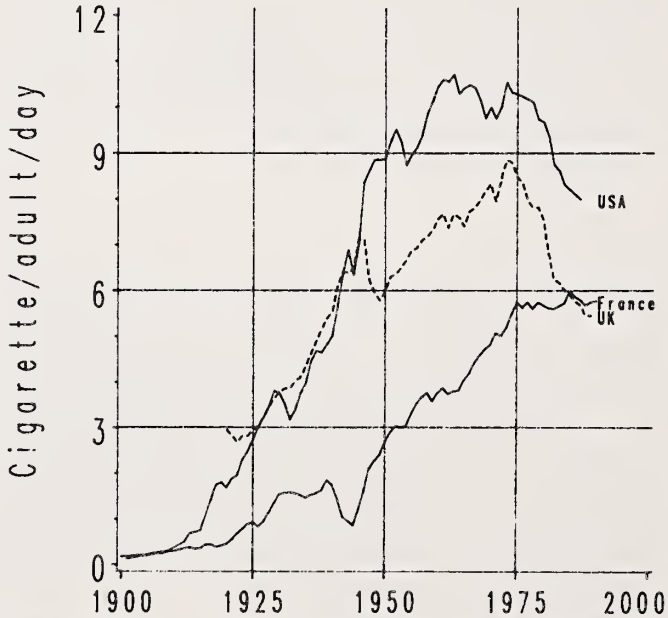


**Figure 3.**—Sales of manufactured cigarettes per population aged ≥15 years. Data from (*1*, *5*, and *6*).

**Table 2.**—Proportion of total tobacco sales represented by manufactured cigarettes

| Country | Cigarettes as percentage of total weight | | |
|---|---|---|---|
| | 1950* | 1970* | 1985† |
| Belgium | 44 | 67 | 77 |
| Denmark | 44 | 59 | 64 |
| France | 61 | 83 | 91 |
| FRG | 37 | 81 | 88 |
| Greece | 100 | 100 | 100 |
| Ireland | 80 | 90 | 93 |
| Italy | 77 | 94 | 99 |
| Netherlands | 33 | 49 | 61 |
| Portugal | 73 | 96 | 98 |
| Spain | 31 | 89 | 94 |
| United Kingdom | 82 | 87 | 87 |
| United States | 70 | 77 | |

*From (*1*).
†From (*9*).

**Table 3.**—Proportion of smokers, ex-smokers, and nonsmokers in adult population, 1987

| Country | Smokers | Ex-smokers | Nonsmokers |
|---|---|---|---|
| Belgium | 36 | 19 | 45 |
| Denmark | 46 | 19 | 35 |
| France | 38 | 22 | 40 |
| FRG | 36 | 18 | 46 |
| Greece | 43 | 11 | 46 |
| Ireland | 33 | 19 | 48 |
| Italy | 33 | 20 | 47 |
| Netherlands | 44 | 22 | 34 |
| Portugal | 33 | 11 | 56 |
| Spain | 41 | 11 | 48 |
| United Kingdom | 37 | 24 | 39 |
| United States | 33 | 27 | 40 |

From (*10*, *11*).

**Table 4.**—Proportion of cigarette smokers by sex

| Country | Males | Females | M/F Ratio |
|---|---|---|---|
| Belgium | 32 | 28 | 1.1 |
| Denmark | 37 | 40 | 0.9 |
| France | 43 | 29 | 1.5 |
| FRG | 40 | 26 | 1.5 |
| Greece | 61 | 25 | 2.4 |
| Ireland | 33 | 28 | 1.2 |
| Italy | 38 | 28 | 1.4 |
| Netherlands | 42 | 39 | 1.1 |
| Portugal | 52 | 14 | 3.7 |
| Spain | 53 | 26 | 2.1 |
| United Kingdom | 34 | 33 | 1.0 |
| United States | 31 | 27 | 1.2 |

From (*10*).

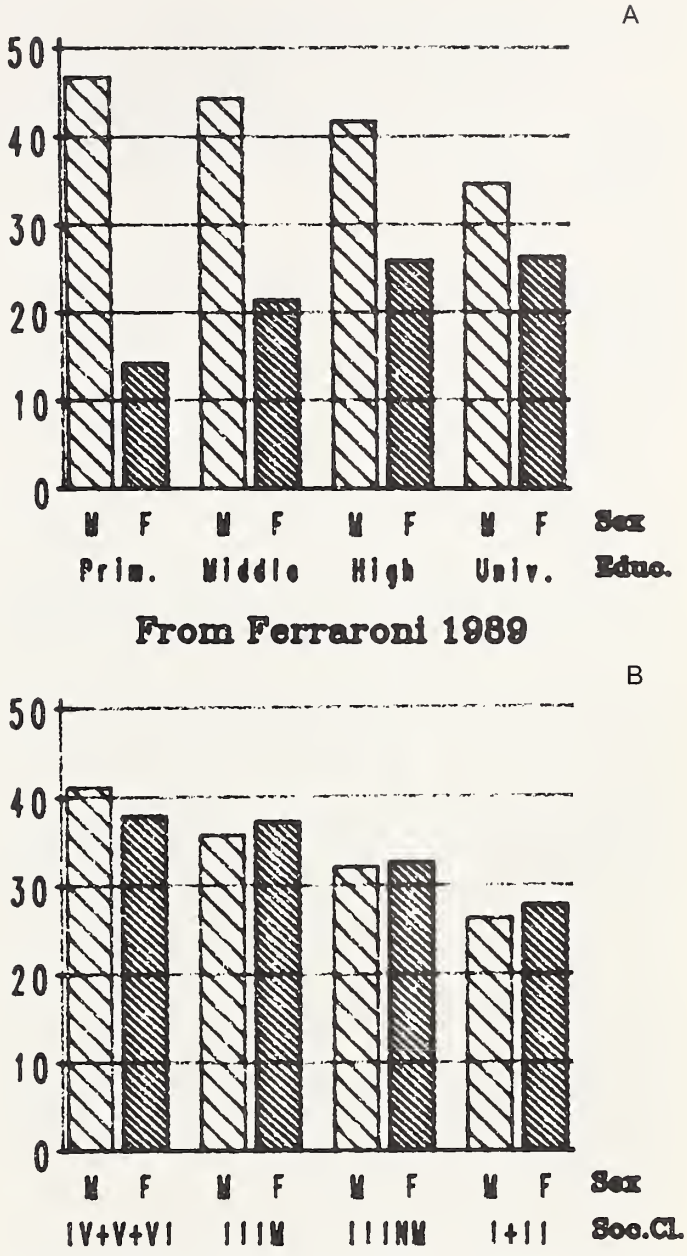


**Figure 4.**—Effect of education or social class on smoking prevalence in Italy (*A*; *3*) and United Kingdom (*B*; *5*). I + II, professionals, employers, and managers; III NM, intermediate and junior nonmanual workers; III M, skilled manual and self-employed nonprofessionals; IV + V + VI, semiskilled, unskilled manual, and personal service workers.

in each country divided by per-capita income (table 5). The European Common Market, calling for some uniformity, should increase cigarette costs in the countries where they are cheapest. Unfortunately, this is not the case. In France, for instance, after the announcement of an increase in cigarette prices in January 1981, described as a public health measure, the increase in price was canceled out by a decrease in tax. The result was that the nominal price of cigarettes remained constant, which represents a relative decrease given inflation.

Table 5.—Price of cigarettes in 1986

| Country | Price of 20 cigarettes/ income, $/$10 000 |
|---|---|
| Ireland | 5.5 |
| Portugal | 3.7 |
| Denmark | 3.4 |
| United Kingdom | 3.3 |
| FRG | 2.2 |
| Italy | 2.0 |
| Netherlands | 1.9 |
| Belgium | 1.9 |
| Greece | 1.4 |
| Spain | 1.3 |
| France | 0.9 |

From (*9*).

## DISCUSSION

The data presented herein are a summary of information from many sources that used a diversity of consumption measures, which complicates the synthesis. Among the problems is the conversion of cigarettes into grams of tobacco. There is no standard conversion factor, although the standards of 1 and 1.2 g of tobacco/cigarette have often been used. A single standard is impossible because the average quantity of tobacco in a cigarette varies with time and among countries. The comparison for Spain of the data from Vioque (unpublished observations) in millions of cigarettes and from Lee (*1*) in grams suggests that, around 1955, a conversion factor of 1.6 was closer to reality than the factor 1.0 used by Lee. The problem is less acute for current consumption, at least in Western countries, because the cigarettes are virtually the same everywhere.

Instead of converting cigarettes to grams, some authors have chosen to convert total tobacco to cigarette equivalents. The underlying assumption is again the standard weight of a cigarette, but this assumption is better hidden, which is not a desirable property.

The consumption of cigarettes or of tobacco in a country can be given per capita or per adult population. The consumption per capita is the total consumption divided by the size of the total population. The consumption per adult is the total consumption divided by the size of the adult population, which is most often defined as the population aged $\geq 15$ years but can be defined as population aged 18+ (*6*) or 20+ (*13*) years. To add confusion, some authors indiscriminately use the notations age $\geq 15$ years and age $> 15$ years.

Another minor complication is that most publications give yearly consumption, whereas I give daily consumption. The conversion is straightforward, but 8 cigarettes/day is easier to interpret than the equivalent 2900 cigarettes/year.

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# US Tobacco Export to Third World: Third World War

Judith Mackay[1]

**ABSTRACT—Global tobacco-related mortality will rise from the current 2.5 million to over 10 million annually by 2050. Most of this increase will occur in developing countries, where legislative controls and other measures that succeed in limiting the use of tobacco in industrialized countries do not exist or are at best inadequate. Of particular concern is the penetration of developing countries by the transnational tobacco companies, with aggressive promotional campaigns that include specific targeting of women, few of whom currently smoke in developing countries. The transnational tobacco companies advertise and market in ways long banned in the United States, for example, selling cigarettes without health warnings, advertising on television, and selling cigarettes with higher tar content than the same cigarettes sold in the United States. Also, tobacco advertising revenue prevents the media from reporting on the hazards of tobacco, a particularly serious problem in developing countries, where awareness of the harmfulness of tobacco is low. The transnational tobacco companies interfere with the national public health laws of developing countries via political and commercial pressures to open markets and to promote foreign cigarettes. This has led to an increase in market share by foreign cigarettes, but evidence also points to market expansion, especially among young people. The entry of the transnationals leads to a collapse of national tobacco monopolies or to their changing from unsophisticated government departments that may still cooperate with health initiatives on tobacco to copying the aggressive marketing and promotional behavior of the transnationals. Thus, the issue is not a simple one of replacement of local by foreign cigarettes but the replacement of an unsophisticated, often rural, industry with a powerful and sophisticated company. [J Natl Cancer Inst Monogr 12:25–28, 1992]**

Global disease, disability, and death from tobacco will increase in the future from the current 2.5 million to about 10 million annually by 2050 (*1*; table 1), and most of this increase will occur in the Third World. In China alone, of all the children alive today, 50 million will die from smoking (*2*).

The Third World cannot afford this increase in either human terms or in economic costs, eg, costs of medical and health care, lost productivity, fires, or the misuse of land. The World Health Organization (WHO) has stated that, in developing countries, the legislative controls and other measures, which in industrialized countries succeed in limiting the use of tobacco, do not exist or are at best inadequate and that the burden on the Third World will actually widen the gap between rich and poor nations (*3*).

Although indigenous production and consumption of tobacco remain major problems in developing countries, the penetration of the transnational tobacco companies is of great concern. As markets decline in developed countries, these companies are targeting developing countries (*4*). It is estimated that sales in Asia alone will increase a minimum of 18% by 2000 (*4*).

## TRANSNATIONAL TOBACCO INDUSTRY TACTICS IN DEVELOPING COUNTRIES

Third World countries have little experience in dealing with the transnational tobacco industry, whose tactics include promotion, political and commercial pressures, and the weakening of national monopolies.

### Promotion and Sales—Double Standard

The transnational companies apply different marketing and promotional standards in Asia than in the United States. For example, although based in countries with long-established television advertising bans, the companies strenuously fought against Hong Kong's ban on television tobacco advertising with a disinformation campaign sponsored by the foreign tobacco companies. Despite stated national regulations in China prohibiting tobacco advertising, advertisements for foreign cigarettes can be seen everywhere. In countries such as the Philippines, cigarettes are promoted and marketed in ways long banned in their country of origin, eg, selling cigarettes without a health warning, advertising on television, and selling cigarettes with higher tar content than the same cigarettes sold in the United States (*5*).

Some of the best examples of the efforts of the transnational tobacco companies to create a market are from Asia. Virginia Slims has been launched in Hong Kong, clearly targeted at young women, showing the usual images of beauty, slimness, and desirability, combined with clear messages of emancipation. However, only about 1% of women under the age of 40 years smoke in Hong Kong, so the number who could switch brands is negligible. This expensive advertising blitz seems a clear attempt to create a market. The same type of promotion

[1] Asian Consultancy on Tobacco Control, Riftswood, 9th Milestone, Clearwater Bay Road, Sai Kung, Kowloon, Hong Kong.

**Table 1.**—Past and future deaths due to cigarettes, estimated worldwide

| Year | Annual deaths (in millions) |
|---|---|
| 1950 | 0.2 |
| 1975 | 1 |
| 2000 | 3 |
| 2025 | 8* |
| 2050 | 12* |

From (*1*).

*Assuming no further large change in proportions of young adults who become regular smokers.

toward women is seen in other developing areas, where only an average 5% of women currently smoke (*6*).

As in the West, youth are another prime target of promotion, with the easily recognized images of health, wealth, macho, glamour, and the outdoors. With few exceptions, cigarette advertisements shown in developing countries promote idealized Western cultures and life-styles, another questionable aspect of tobacco advertising in the Third World.

Studies in Western countries dating back to the 1930s provide evidence that cigarette advertising revenue has repeatedly led to suppression of the media from reporting on tobacco and health to the extent that the problem warrants (*7, 8*). Anecdotal evidence from developing countries supports this evidence. For example, health workers in many Asian countries report difficulties in obtaining television coverage on tobacco issues on television stations that run tobacco advertising. This is of particular concern in developing countries, where knowledge of the harmfulness of smoking is often low or nonexistent.

Sponsorship, again predominantly or exclusively by foreign tobacco companies, builds a constituency of thankful and financially dependent recipients in developing countries who can often be relied on to support the tobacco industry.

### Political and Commercial Pressures

The foreign cigarette companies attempt to interfere with the national public health laws of developing countries. One example of this was seen in 1986 when the government of Hong Kong attempted to ban smokeless tobacco. To kill the Hong Kong ban, the tobacco industry mobilized the US Commerce Department, the State Department, some US senators, the American Chamber of Commerce in Hong Kong, and a powerful Hong Kong legal firm.

In an October 1986 letter to Hong Kong's Chief Secretary, Senators R. Dole, C.J. Dodd, B. Kasten, and L.P. Weicker, Jr., said the ban "would constitute an unfair and discriminatory restriction on foreign trade—at least that is the way it is likely to be viewed in the United States." The senators said the ban could cause "a potential barrier to our people's historic trade relationship," words to make any US trading partner tremble.

The Hong Kong government stood firm in pursuing responsible public health policy and, in January 1987, Hong Kong became only the second location in the world to ban the manufacture, importation, and sale of smokeless tobacco products. The government was able to resist the contents of the senators' letter by rightly claiming that this did not constitute a ban specifically against a US product, because import from any country and manufacture within Hong Kong itself were banned.

Japan provides another example. In July 1986, Senator J. Helms wrote to the Japanese prime minister expressing concern that "American cigarettes still claim less than 2% of the Japanese market." Helms concluded,

> Your friends in Congress will have a better chance to stem the tide of anti-Japanese trade sentiment if and when they can cite tangible examples of your doors being opened to American products. I urge that you make a commitment to establish a timetable for allowing US cigarettes a specific share of your market. May I suggest a goal of 20% within the next 18 months.

No other US export product was mentioned in Helms' letter.

By late September 1986, the US administration had prepared a list of retaliatory tariffs on Japanese exports. In October, Japan conceded to the demand to end its tariff on foreign cigarettes. A Philip Morris spokesman said, "The suspension of the tariffs in Japan and the recent opening of the market in Taiwan are the direct result of effective negotiations by the Office of the US Trade Representative" of the US government (*9*). Thailand has recently been at the center of another trade threat in a successful attempt, via the General Agreement on Tariffs and Trade (GATT), to open the Thai market to US tobacco products.

For an industry that so often speaks of freedom, the political coercion of threatened trade sanctions is noteworthy. The tobacco companies make no apology for this. R.J. Reynolds even said, "We expect such support [from the US government]. That's why we vote them in" (*10*).

These pressures have led to protests in Asia against US tobacco export policy, with demonstrations on the streets, antiforeign posters, and outrage expressed in the media and in medical journals (*11*).

### Effect on National Monopolies

Other tactics by the transnational tobacco companies have been to form subsidiaries and pressure countries to denationalize state monopolies, usually in four stages: *1*) When foreign companies enter a country, there are offers of help with technology in farming and manufacturing, free trips overseas, and coproduction of glossy magazines. *2*) Next come the joint ventures, in reality a "foot in the door." At this stage, advertising and promotion by the foreign companies have begun to creep in, usually of a sophistication unknown to the national monopoly. *3*) The relationship then becomes less harmonious, with accusations that a monopoly prevents free market access and with the trade threats already described. Because of the political strength of the foreign companies,

the national monopoly usually must accede to their demands. *4*) Finally, the national monopolies weaken or may be disbanded. Even more worrisome is the way some monopolies have turned quasiprivate and have begun copying the behavior of the transnationals, eg, in Japan and more recently in Indonesia.

## WHY TRANSNATIONALS ARE SO IMPORTANT

The tobacco industry argues, what does it matter what people in the Third World smoke? They claim the issues are of fair trading and market share and not health. It matters for several reasons.

*1*) There is emerging evidence that the opening of the markets is not only leading to a sharp increase in market share of foreign cigarettes but is also leading to increased smoking among youth in these countries (*12, 13*). Thus, the issue is not simply replacing local with foreign cigarettes but also market expansion, with the targeting of women being of particular concern.

*2*) There is a replacement of a simple, unsophisticated, often rural industry with a powerful, sophisticated, transnational company. This replacement is not just a neutral matter of free trade but may also become a substantial determinant of current smoking patterns and, hence, of future disease.

*3*) The denial of the health evidence and the challenge of effective health initiatives by the transnational tobacco companies contrast with the current stand taken by some of the national monopolies. For example, the commercial transnational cigarette companies continue to issue statements such as: "The fact is, that smoking has not been scientifically established as the cause of any human disease" (*14*). They have flown "experts" to Hong Kong and the Philippines to speak to government and other officials in an attempt to prevent antitobacco legislation being passed. In contrast, the Chinese National Tobacco Corporation is, at least in part, cooperating with health initiatives on tobacco currently being undertaken by the Ministry of Public Health, including antitobacco legislation and even funding certain health initiatives.

*4*) Profits from selling foreign tobacco do not benefit the Third World but are instead returned to the shareholders in the West. Thus, the introduction of foreign cigarettes can cause loss of foreign exchange.

*5*) Third World governments are often preoccupied with other general or health problems, eg, high infant mortality and communicable diseases. These factors, combined with a virtual absence of policy, laws, health education programs, and tax policy on tobacco in some developing countries and a lack of experience in dealing with transnational tobacco company tactics, can leave countries open and vulnerable to penetration by a foreign industry.

*6*) The same intent toward eastern Europe is already evident in the tobacco companies' recent tactics. At an International Union Against Cancer conference titled "A Tobacco-Free New Europe," held in Poland in November 1990, participants expressed grave disquiet at both the economic impact and health problems the new democracies will face as the transnational tobacco companies are allowed access into their markets. Reports from Warsaw, Budapest, Moscow, and Prague, where cigarette advertising is still illegal, showed that the Western tobacco companies are ignoring the law and placing their trademarks everywhere (*15*).

## A NOTE OF OPTIMISM

### In Developing Countries

Developing countries must take their own action against tobacco, but many still lack the basic prevalence data to understand the scope of the problem in their own countries. In the Far East, countries including China, Malaysia, Hong Kong, Korea, and Thailand have established national coordinating organizations on tobacco control. Singapore, Indonesia, and the Philippines have active health societies. Most countries in Asia have initiated health education and some legislation over the last decade. In general, however, these measures lag far behind those taken in Western countries. Developing countries are entering a crucial decade in initiating attempts to reduce the future health effects of the tobacco epidemic. At the moment they seem poised to do this, the transnational companies are presenting a formidable opposition.

### In United States, United Kingdom, and Other Exporting Countries

Antismoking efforts in the United States and United Kingdom are being neutralized by the increase in smoking in poor countries. For every smoker who quits in the United States, two teenagers start smoking in China. Health societies in the United States and United Kingdom have assisted by bringing these issues to public and government attention and can continue to do so by lobbying for the following recommendations:

1. US and UK tobacco companies and their subsidiaries should, at minimum, adhere to the same standards of product, marketing, promotion, and sales in developing countries as are required in the United States or the United Kingdom.
2. US and UK tobacco companies should cease lobbying and pressuring governments of developing countries to prevent the passing and implementing of antitobacco measures.
3. The US government should desist from helping the US tobacco companies with export activities. It should become unacceptable and illegal to threaten or invoke trade sanctions in relation to tobacco.
4. US and UK expertise in countering the tobacco epidemic should be shared with developing countries so that, instead of the United States and United Kingdom exporting death and disease, they become exporters of health.

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# Worldwide Expansion of Transnational Tobacco Industry

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**ABSTRACT—As smoking rates fall in North America and western Europe, transnational tobacco companies (TTCs) from the United States and Great Britain turn to cigarette markets of the developing world to replace those smokers who have quit or died from smoking. The majority of these markets are dominated by state tobacco monopolies that advertise and promote smoking minimally. Few women or adolescents smoke in those nations. The majority of men do, but they smoke far fewer cigarettes per year than their counterparts in developed nations. Trade barriers in the developing world prevent foreign cigarette companies from entering. TTCs employ various techniques to force open those markets, including trade pressure from the US government. Once the market is open, Western cigarette advertising and promotions target nonsmoking women and children. Retail tobacco outlets increase, smoking rates rise, and more death and disease result. Latin America was the TTC target in the 1960s, the newly developed nations of Asia during the 1980s, and, today, the tobacco giants are pushing into eastern Europe, China, and Africa. If nothing is done, emerging national smoking-control programs will be overwhelmed, and state-owned cigarette monopolies will be taken over by the TTCs. Policies and programs to curb smoking exist, but for various reasons many lesser developed countries have not adopted them. The threat of TTC entry into a closed market offers an opportunity to form national coalitions against smoking, educate the public about the dangers of tobacco use, and implement public health policies and programs to restrict marketing and use of cigarettes. Recently, Thailand resisted threat of US trade sanctions, and, ruling in the case, the world's international trade body, the General Agreement on Tariffs and Trade, found that nations had the right to limit trade of harmful products to protect health so long as policies were nondiscriminatory. Acceptable policies include the following: eliminate marketing practices that fuel cigarette consumption, require bold warning labels, raise price through taxation, limit distribution, and ensure clean air for nonsmokers. As markets are opened over the next decade, these public health policies and programs must be erected before the TTCs can dominate these markets. [J Natl Cancer Inst Monogr 12:29–35, 1992]**

An estimated 1 billion people smoked 5.2 trillion cigarettes worldwide in 1988, and during the same year 3 million died from diseases caused by smoking (*1*). Most of these deaths occurred in the developed world, where smoking rates are declining 1.5%/year. Rates in developing nations, however, are rising 2.1%/year, an increase that will result in a future epidemic of smoking-related death and disease occurring in the Third World (*1*).

Prevention of this epidemic is the single greatest challenge to the world's public health community, and interventions exist to curb smoking worldwide. History shows that, as a nation's economy improves, consumers have more disposable income to buy cigarettes. Urbanization and industrialization also lead to an increase in tobacco use, and smoking becomes more popular with women as they enter the work force. These forces can be countered with such measures as raising cigarette prices through taxation, banning public smoking, or restricting advertising that promotes the practice.

These measures have not been uniformly adopted in the developing world, a failure that is due to the strong economic grip of tobacco on poor nations' economies (*2*, *3*). According to a 1983 study of 69 countries (90% of the world's population), tobacco agriculture, manufacture, and sales produced 28 million jobs that year and generated $129 billion in sales of which $79 billion was tax revenue (*4*). This economic dependence was particularly strong for developing nations: 4.7% of total taxes in Africa and Latin America were collected from tobacco sales, which represented 5.5% of total retail sales in Latin America and Africa versus 3.6% in North America and Europe. Many poor countries are also overwhelmed dealing with the immediate problems of infectious disease and malnutrition and have had little experience with the multinational tobacco companies.

External pressure from the tobacco companies of the United States and the United Kingdom compound this problem (*3*). The world's six transnational tobacco companies (TTCs) are penetrating Third World cigarette markets, and their entry triggers competition with the national companies, resulting in the introduction of new marketing techniques that increase consumption. These include "American" blended cigarettes whose "lighter" tobacco makes the start of smoking easier for nonsmoking women and children and increases the number of cigarettes smoked per day by those who already smoke. Other changes occur in the market (ie, price competition, expansion in retail outlets, specific brands for women, and sophisticated advertising and promotions), all of which increase consumption (*3*, *5*).

This article describes the world tobacco industry and discusses how multinational cigarette companies penetrate and transform the closed markets of the Third World. It

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also addresses the ways in which the conflict that develops between TTCs and local governments can be used to pass policies that both curb smoking and protect local tobacco companies from exploitation by TTCs. If these policies are adopted, millions of lives will be saved.

## STATUS OF WORLD CIGARETTE MARKET

### Tobacco Leaf Production and Cigarette Production

In 1988, 7.2 million tons of tobacco leaf were grown worldwide, a figure that was up 7.5% from 1987 (*4*). The 1983 market value of tobacco leaf was $11.3 billion. The Food and Agriculture Organization (FAO) (*6*) predicts that production will increase 2%/year over the next 10 years: that of developing countries growing at a rate of 2.4% and that of developed countries at 1%. The centrally planned economies of China and eastern Europe produce 43% of the world's leaf, the United States produces 13%, and the western European nations of Italy, Turkey, and Greece produce 9% (*7*). Brazil, Malawi, and Zimbabwe are the principal sources of tobacco for TTCs and produce 18% of the world's total. Indonesia, Korea, Japan, Thailand, India, and the Philippines produce tobacco that is generally used by their state companies. Two-thirds of the world's tobacco is grown in developing countries, and about 20% of all tobacco is exported onto the world market (*6*).

In 1988, 5.2 trillion cigarettes were produced: 1.2 trillion (23%) in China, 1 trillion (21.3%) in the Americas, 700 billion (13.4%) in western Europe, 730 billion (14%) in Asian nations other than China, and 700 billion (14%) in eastern Europe (*7*, *8*). Only 10% of manufactured cigarettes are exported onto the world market, but an estimated 10% are sold internationally as contraband (*5*). Forty percent of all the world's cigarettes are manufactured by the six TTCs, and the retail value of all cigarettes sold in 1983 was $138 billion (*4*).

### Transnational Tobacco Companies

The invention of the cigarette rolling machine in the 1880s introduced mass cigarette production and resulted in the emergence of modern cigarette companies. A handful of companies quickly controlled cigarette manufacture in the United States and the United Kingdom, and these exist today as transnationals (*5*).

Smoking-control campaigns in the United States had several unintended effects on the industry. First, bans on television advertising precluded new cigarette companies from entering the market and resulted in the formation of an oligopoly of manufacturers with little real competition occurring among them. Restrictions on advertising and public education campaigns forced the industry to develop new creative cigarette marketing techniques to circumvent the restrictions and undermine public knowledge about the dangers of smoking. These techniques are available for use in the developing world, where little is known about the dangers of smoking and where cigarette advertising by the state monopoly or national company has been minimal.

As smoking declined in the 1960s, the US companies were forced to look for new markets, first in Latin America and later in western Europe. With the further decline in the 1980s, these companies turned their attention to the closed markets of Asia and eastern Europe (table 1).

The six major TTCs include British American Tobacco (BAT, UK), Philip Morris (PM, US), R.J. Reynolds Nabisco (RJR, US), American Brands (AB, US), Rothman's (UK, South America), and Imperial Tobacco (UK). The first two are the largest and produce 22% of the world's cigarettes (*9*). PM held one-third interest in Rothman's, which it sold in 1989 (*10*). These companies and their 90 subsidiaries produce approximately 40% of the world's cigarettes. If nations with state-owned tobacco monopolies and centrally planned economies are excluded, the number rises to 85%. TTCs effectively control 85% of the tobacco leaf sold on the world market and, in doing so, indirectly determine the price of the cigarettes from which they are made.

The 1988 annual reports of the four largest US cigarette companies (PM, RJR, AB, and Loews) show combined 1988 sales of $71 billion, of which $32.5 billion (46%) were for cigarettes. Half of these sales were international. The four companies reported profits of $10.9 billion in 1988, of which tobacco was $7.2 billion or 66% of all profit (*11*). This high profitability comes from US cigarette sales and is due to low US excise taxes and the collective price-setting policies of the companies. Profits from a pack of US-sold cigarettes are three times higher than those sold abroad and three times greater than company profits from the sale of nontobacco products in the United States. The US excise tax is the lowest of all developed nations, 32% of price versus 55% among the 22 developed countries.

The beneficiaries of TTC expansion worldwide are the stockholders. All four US producers are public companies owned by shareholders. Approximately 60% of these four companies' shares are held by institutional investors, such as public pension funds, insurance companies, college endowments, banks, and investment firms. Ironically, many of these institutions exist to promote health and well-being

**Table 1.**—Cigarette market share by TTCs in various regions

| Region | Date of entry | Current share, % | Regional volume* |
|---|---|---|---|
| North America/United Kingdom | 1900 | 99 | 900 |
| Latin America | 1965 | 75 | 400 |
| Western Europe (excluding UK) | 1970 | 40 | 550 |
| Newly developed countries of Asia | 1980 | 15 | 450 |
| Eastern Europe | 1990 | 3 | 1000 |
| China | 1995 | 2 | 1400 |
| Other closed markets | 1995 | 5 | 400 |

*In billions of cigarettes; does not include contraband.

but are drawn to the high profitability of the tobacco industry (*11*).

In 1976, PM reported net sales of $3 billion for tobacco products, of which $1 billion were international. In 1988, total cigarette sales rose fivefold to $16.5 billion, of which $8.5 billion were overseas, representing an eightfold increase (*11*). RJR predicts that it will more than double its tobacco sales from 1988 through 1998 (from $7 billion to $16 billion) and triple its profit from tobacco (from $2.8 billion to $8.2 billion) (*12*).

TTCs generally conduct their business through local subsidiaries or, if they are prevented by local law, through joint manufacturing or licensing agreements with local companies. For example, BAT has 90 factories in 40 countries and sells 80% of their cigarettes in the producing countries. BAT has 10 subsidiaries in Africa, 13 in Latin America, and 8 in Asian countries and holds 90% interest in these companies (*9*). PM has 11% of the world's market and reports that it has a 10% share of the market (74 billion of 780 billion cigarettes) in the 37 developing countries in which it does business. In 7 countries, PM has a subsidiary, in 18 it has a local licensee, and in 12 it has direct import agreements (*13*).

The expansion also helps the US trade deficit. In 1988, the United States realized $3.5 billion in trade surplus from tobacco exports, which was up from $2.5 billion in 1987 (*14*). However, US tobacco farmers have benefited minimally. The value of US-grown tobacco sold in exported cigarettes or as whole leaf rose from $1.3 billion in 1980 to $1.5 billion in 1988 (*15*). During the same time, the value of cigarette exports by PM, RJR, and AB tripled from $1.1 billion to $2.9 billion (*10*, *12*).

### State Monopolies and National Cigarette Companies

Many countries operate closed cigarette markets and restrict sales of cigarettes to those produced by their monopoly or national firm to prevent loss of scarce consumer capital for a nonessential foreign good (*3*, *5*). About half of all the world's cigarettes are sold in closed markets (*12*).

Of the world's major state monopolies, the Chinese monopoly is the largest and produces 1440 billion cigarettes or 22% of the world's total. Eastern European monopolies produce about 700 billion (14%), and western European monopolies produce 230 billion (5%). Other major Asian monopolies or national firms account for 600 billion, 11% of world production, and include Japan (260 billion), Indonesia (115 billion), Korea (82 billion), Thailand (30 billion), Taiwan (28 billion), and Vietnam (25 billion) (*16*). The markets of sub-Saharan Africa, excluding South Africa, are relatively small, with only 50 billion cigarettes produced in 1988 (1% of the world's total). Latin America's market produces 300 billion units annually, and was initially composed of monopolies and national firms. TTCs entered that market in the late 1960s and subsequently dominated and acquired the companies. Seventy percent of the former Latin American monopolies are now TTC subsidiaries (*5*).

Monopolies are considered inefficient in comparison with the TTCs. They generally produce a less "flavorful" cigarette that uses harsher local leaf (*16*). In the absence of competition, there is generally no cigarette advertising. These marketing inefficiencies may have the unintended public health benefit of curbing smoking. The smoking prevalence in many of these countries is similar to that found in the United States 30 years ago. High smoking rates are found among adult men and low rates among women and adolescents. Fewer cigarettes are smoked per day than in the Western markets. For example, in Japan and China, smoking rates for men are approximately 60% and rates for women are 12% and 7%, respectively. Per-capita consumption is 1200 cigarettes/person per year in China, 1600 in Taiwan, and 1800 in Korea. The US rate is 2600 cigarettes/person per year (*17*).

## EXPANSION INTO DEVELOPING WORLD

### Market Protection

Many monopolies protect themselves from foreign competition by protective trade measures that include bans on foreign imports. Other less overt measures include high tariffs, import quotas, and restrictions on distribution and advertising of foreign brands. This may be equally effective in keeping out foreign competition (*5*, *16*).

Removal of these barriers and securing cigarette advertising guarantees are the main objectives of the TTCs (*14*). To do so, multinationals directly approach local cigarette companies to sell their international brands through a license or joint manufacturing agreement. The TTCs argue that this arrangement keeps money in the country and helps the state company by making it more competitive by providing modern tobacco agricultural and manufacturing techniques (*15*).

Many nations still refuse to deal with the multinationals. In this case, contraband cigarette sales occur as a market-softening technique. Shepherd (*5*) observed that multinationals used their international brands as a lure to gain a foothold in the market and stimulate local demand. The loss of tax revenue from bootlegging served as an added incentive for local governments to legalize foreign brands. This tactic is still being used and is a major problem throughout all of the markets of Asia, particularly in the closed markets of China, Vietnam, and Thailand (*14*). Brands such as Marlboro and Camel convey powerful images of Western life-style and success.

### Politics and Market Access

Multinational companies have also applied political pressure to gain entry. According to a 1976 Securities and Exchange Commission report, PM and RJR made $2.8 million in "questionable payments" in their Latin American operations in the 1970s. In at least seven countries, payments were made to government officials to secure favorable agreements relative to their market operations (*3*).

External political pressure is also used. In 1986–1987, US cigarette companies asked key members of Congress to pressure the trade officials of Korea, Taiwan, Japan, and

Thailand to open their cigarette markets (*18*, *19*). The congressmen threatened these countries with the passage of protectionist US trade legislation unless tobacco trade barriers were removed. In the case of bans of all smokeless tobacco products in Hong Kong, Ireland, Australia, and the United Kingdom, one TTC (US Tobacco) had 147 members of Congress urge the US trade representative to use trade sanctions against these countries if they refused to remove their bans. The company contributed $75 000 to the political campaigns of 40 of the legislators (*20*).

Former US administration officials have also been involved. In 1985, Michael Deaver, former chief of staff to President Reagan, was paid $250 000 by PM to secure trade concessions from Korea on cigarettes. Michelle Laxalt, daughter of Senator Paul Laxalt, was also hired by PM. Richard Allen, former US national security director, was hired to do the same by RJR. At a meeting with the president of Korea, Deaver said he would take care of pending US protectionist legislation that would hurt Korea's textile industry if Korea opened its market to US cigarettes (*21*). A few months later, President Reagan vetoed the protectionist Jenkins-Thurmond Textile bill and Korea unilaterally opened its cigarette market.

### Tobacco Trade Threats and Sanctions

Another strategy to force open a closed market is the use of retaliatory trade threats by the US government. In 1984, Congress amended section 301 of the 1974 Trade Act to allow the president to conduct investigations of alleged unfair trade practices against US products by foreign countries. At the request of the US Cigarette Export Association (USCEA), which represents PM, RJR, and Brown and Williams, the US government conducted four investigations on the tobacco trading practices of Japan, Taiwan, Korea, and Thailand from 1985 to 1990 (*22*, *23*).

The US trade representative threatened these nations with sanctions on goods they export to the United States unless our cigarette companies were given free access to their markets. Japan, Korea, and Taiwan capitulated to US demands. Japan and Korea were also pressured to denationalize their tobacco companies. Trade threats were also used to expand advertising and promotional opportunities. Both Taiwan and Korea were pressured by the US trade representative to repeal restrictive measures on cigarette advertising, including bans on television cigarette advertising, which is illegal in the United States. Both countries refused to allow television advertising but, under pressure, did allow print cigarette advertisements. Japan moved to restrict television cigarette advertising, but delayed action at the request of the US Trade Office (*23*).

### Modernization of Local Industry

Once a market is opened, capital and technology are required to expand tobacco agriculture, construct and modernize manufacturing plants, and establish the groundwork for introducing modern cigarette marketing practices. During the 1970s, the United States exported over $1 billion in tobacco leaf to the developing world as part of the US Food for Peace program (*3*). These exports helped strengthen local cigarette manufacture and increase the demand for American blended tobacco. The inclusion of tobacco in Food for Peace ended in 1982.

A new US program, the Export Credit Guarantee, was begun in 1982 to give export guarantees for US exported tobacco leaf. From 1984 to 1988, $188 million in credits were allocated for Iraq, Egypt, Turkey, and Algeria (*24*). This program has helped to advance TTC interests in the Near East. As an example, PM constructed a new joint manufacturing plant in Turkey in 1989 and used the credit program as a lever to enter that closed market. PM is constructing a new $100 million cigarette plant in Turkey.

Other sources of funding include international development agencies such as the World Bank and FAO. From 1972 to 1983, the World Bank provided $640 million in loans for tobacco agriculture (*25*). The World Bank recently ended new funding for tobacco and is now actively funding projects to curb smoking in China.

Capital for cigarette manufacture and advertising is readily available from the high profits that TTCs realize from cigarette sales in the developed world. Since 1982, US tobacco companies have collectively increased prices by 58% while inflation has risen only 27%, thus substantially increasing their profit. Four US companies made more than $10 billion in profits in 1988 in US cigarette sales alone (*11*), which have provided the needed revenue for overseas expansion. For example, RJR recently constructed a $21 million plant in China to produce 6.5 billion cigarettes for that country (*19*). PM intends to put $2.5 billion into capital for its foreign tobacco operation over the next 5 years (*10*).

### Buying Favor With Local Governments

The TTCs ingratiate themselves with developing countries by providing support for social and cultural projects. For example, BAT constructs schools and provides scholarships for students in Zaire, Malaysia, and India (*26*). BAT also funds environmental projects in Costa Rica, Uganda, and Indonesia and supports cultural projects designed to maintain national heritage in Venezuela, Nicaragua, and Zimbabwe.

PM contributed $220 000 to the Mexican Pan American Development Fund and is the principal sponsor of the Ixchel Museum in Guatemala. PM estimates that it employs 11 000 people in Latin America, 7300 in Africa, and 7400 in Asia. PM also funds training for 1000 physiotherapists in China and supports the Save the Children project in Ethiopia that provides food, medical supplies, and clothing. According to PM, in the Third World, "Often enough, our support is all there is" (*13*). PM is sponsoring a Russian art exhibit at the New York Metropolitan Museum and the Bolshoi Ballet in Hawaii.

### Introduction of Cigarette Advertising and Promotions

Transforming a closed market into one that is competitive results in the introduction of cigarette advertising on a massive scale. This is best seen with the recent entry of

TTCs into Asia. Two years after TTC entry into Japan, a 10-fold increase in television cigarette advertisements occurred (*17*). Cigarette advertisements now rank second on Japanese television in terms of total minutes of airtime. Japanese retail sites that sell cigarettes have also been greatly expanded, particularly vending machine operations. In Taiwan, hundreds of small shops have been contracted by US companies both to sell their brands and conduct point-of-purchase advertising as sidewalk advertisements for cigarettes (*17*, *19*, *23*).

Beginning in 1986, product promotions, which are rarely done by Oriental monopolies, were introduced on a wide scale. Today, it is common to see young women giving free samples on the streets of Tokyo and at discos popular with young people in Taiwan. Multinational tobacco companies sponsor motorcycle racing and dance troupes in China. Commercials for Virginia Slims cigarettes began airing on Tokyo television in 1987, and a similar targeting of nonsmoking women is under way in Taiwan and Hong Kong (*24*).

The same promotions are occurring in eastern Europe today. In former East Berlin, young women give away free samples of Marlboros and Camels, and Camel car races are being sponsored throughout the region. In the USSR, the Camel Trophy Cup was sponsored by RJR and took place in venues as distant as the Mongolian border. PM sponsors Marlboro Week in Budapest and affixes their logo to the art and social functions they sponsor. Other examples of indirect TTC advertising are widespread. In Warsaw, trolley cars are covered with Marlboro logos (*27*).

In countries such as Malaysia, where television cigarette advertising is not permitted, local subsidiaries and licensees of the TTCs take out advertisements for Kent Holiday and Tours of Marlboro Country to circumvent the ban. In 1989, PM paid $350 000 to have their Lark cigarettes (a brand they sell only in Japan) displayed in a James Bond movie and conducted a special promotion of the brand in Japan when the movie opened (*28*). Bond is popular among Japanese teens. The TTCs deny targeting nonsmoking groups, but this targeting of nonsmoking Oriental women and youth is a clear signal of the multinationals' actual intent.

### Denationalization of Local Companies

Shepherd (*5*) found that the multinationals gradually penetrated a closed market by entering into a series of manufacturing arrangements with the national company. Through this process, the multinationals progressively gained more control over the national company and the market. The first step was to enter into a licensing arrangement with the state firm to sell international brand-name cigarettes. This "foot-in-the-door" approach was tolerated by local policy makers because local leaf was used and cigarettes were produced by the national company. This arrangement did not threaten local farmers or other tobacco workers. Joint manufacturing ventures between the state company and multinationals usually followed, giving the multinationals a firmer foothold and, in exchange for trade agreements, the TTCs gave advanced agricultural and manufacturing technology to the local company. At the same time, the TTCs pushed the local governments to denationalize the state tobacco monopoly and form a private firm. This action removed any residual sentiment that the government may have had for protecting the national company and set the stage for its future acquisition by the multinationals.

As of November 1990, RJR had licensing arrangements in six countries and agreements to conduct joint manufacturing in Hungary and the USSR for its Camel and Winston brands. RJR has also purchased the Berlin cigarette factory of the former monopoly and plans to manufacture there. PM purchased the largest East German cigarette plant in Dresden and plans to demolish it and construct a modern facility to produce 10 billion cigarettes/year. PM has licensing arrangements with six other countries and plans to conduct joint manufacturing with the Soviet monopoly (*27*). In all likelihood, these firms will be privatized and organized by the TTCs.

### Economic Impact for Local Tobacco Industries

Shepherd (*5*) analyzed the denationalization of the Latin American market and the entry of the TTCs. He found that, rather than the state monopoly becoming more competitive in an open market, most Latin firms were seriously weakened by the multinationals. Based on the economies of scale, the locals were unable to compete with the intensive advertising programs and short-term predatory pricing practices of the TTCs. By 1976, the TTCs had formed 12 subsidiaries in 17 Latin American countries. These subsidiaries controlled 90% or more of the market share in their respective countries, most of which were acquisitions of former national companies.

The same is occurring in Asia. Foreign companies that had virtually no share of the cigarette markets now hold 11% of Japan's market, 12% of Taiwan's, and 6% of Korea's; they are expected to control 20%–30% of the markets of all three countries by 1995 (*18*).

### Adverse Effects on Public Health

Multinational cigarette companies have argued that their intention overseas is to encourage smokers to switch to their brands and not to target nonsmokers or increase consumption. Shepherd (*5*) found that, following their entry into Latin America, TTCs greatly expanded promotion and advertising. In Argentina, per-capita advertising expenditures rose 30% from 1968 through 1975. As a consequence, per-capita cigarette consumption rose an average of 6.4% from 1966 to 1975, a rate that is almost three times higher than the 2.4% annual rate increase reported for the year before TTC entry.

In Taiwan, cigarette consumption was declining until the entry of the Western companies and rose 4% in 1987. Korea's consumption also rose 2% 1 year after the multinationals appeared, and a Japanese decline that was occurring before the entry of US firms halted in 1986 and rose 3% during the first 6 months of 1989. A Japanese

survey of smoking among women found that female college freshmen were four times more likely to smoke than their mothers (*17*).

Peto has estimated that of all the people now alive in the world, 500 million will be killed by cigarette smoking. Of the world's children, 200 million will die prematurely from smoking, two-thirds of whom live in the Third World. Many of these children will die after smoking cigarettes rejected by the youth of America and manufactured by US cigarette companies.

**What Can Be Done?**

In theory, if the cigarette markets of the developing world were off limits to the TTCs and if the markets stayed noncompetitive, health officials would have a much easier time implementing educational and policy interventions without interference from the multinational cigarette industry. However, as world trade becomes freer, import bans on foreign cigarettes will be gradually eliminated. The differences between the cigarettes of a multinational and those of a monopoly may not be sufficient to warrant unequal treatment. Both types kill the consumer if used as intended. Equal treatment can be afforded, however, to cigarette marketing in which real differences exist between local and multinational companies. If advertising and promotions are banned, the TTCs lose the ability to rapidly penetrate a market. Short-term economic protection will be afforded to the state company and long-term protection to the nation's health.

Restrictions include bans on advertising and promotions, limits on the number of retail outlets, price control, and the use of ad valorem taxes. However, developing countries face internal resistance from their local industries to the adoption of such policies. The external threat of TTC entry eliminates this and ironically results in local tobacco industries supporting policies that curb smoking. Enormous external pressure still remains. The US Trade Office, in the amended section 301 of its 1974 trade act, prevented passage of policies that would have restricted TTC marketing in three Asian nations. When an economically powerful country such as Japan gives in to such demands, a precedent is set that weaker countries must quietly follow.

This position was challenged in a recent action by the government of Thailand when it became the fourth nation to be accused of unfairly restricting import of US cigarettes and cigarette advertising. In April 1989, the USCEA petitioned the US Trade Office to investigate Thailand's closed cigarette market under section 301 and, if discrimination was found, to compel Thailand to allow imports, reduce tariffs, repeal laws banning advertising, and expand distribution (*14*). The US trade representative acted on the case, triggering a backlash of strong protests by health groups in the United States and Thailand. Members of Congress opposed to the tobacco trade policy forced the US trade representative to hold a public hearing in September 1989. Virtually all major US health organizations testified against the petition, and the national media widely covered the story. In response to the adverse publicity, the US trade representative referred two sections of the investigation (the import ban and tariffs) to the General Agreement on Tariffs and Trade (GATT) and waited to act on the advertising and distribution until GATT made a finding.

GATT established a three-member trade-resolution panel that was charged with finding whether these measures were in violation of GATT articles (*29*). The panel heard from the US trade representative, Thailand, and the World Health Organization (WHO).

In November 1990, GATT issued its ruling and stated that Thailand must allow cigarette imports. This appeared to be a victory for the world cigarette industry. However, GATT went on to delineate nondiscriminatory policies that Thailand could adopt in lieu of a ban that would keep competition out of the market and be consistent with the GATT articles. These included ad valorem taxes, advertising bans, price restrictions, ingredient disclosures, strong warning labels, and even a ban on brand names and imagery.

Many of these measures were still under negotiation with the US trade representative under the unilateral section 301 negotiations. GATT's reference to these measures undercut the US trade representative's ability to secure unilateral concessions. Shortly afterward, the US trade representative dropped the section 301 case. Thailand responded by opening the market but switching its tax from an excise tax on each cigarette to an ad valorem tax based on price, having a greater impact on the more expensive foreign cigarettes than on Thai brands. A comprehensive tobacco control bill was filed that included a total ban on advertising and promotion, prominent warning labels, and a multimillion dollar national smoking-control program. Ironically, this comprehensive package is exactly what US health groups have advocated for in the United States but have been unable to pass because of the political influence of TTCs with Congress.

This was the first GATT decision on a manufactured tobacco product and it has set a critical precedent for other countries. The US trade representative will probably not accept future section 301 tobacco petitions. The GATT action represents one of the most important achievements for international tobacco control in this decade. It is a clear message from the world's trade body that developing nations have the right to protect health by keeping their cigarette markets noncompetitive. To the credit of WHO, the ruling was based largely on its recommendations for curbing smoking in the Third World.

The GATT decision has broad applications. Japan, Korea, and Taiwan were recently forced to allow advertising under trade threats; they can now consider new laws to ban advertising and promotions. The TTCs are pushing into the markets of eastern Europe with new manufacturing arrangements and advertising campaigns. If they are successful, chances to curb the enormous smoking problem of the East will be lost. Scarce consumer capital should go into rebuilding the economies of the East and not be blown away in foreign tobacco smoke. The GATT findings can do this. Other nations (eg, China and India)

will face challenges from the multinationals during the mid-1990s, and the GATT rulings provide them with a proper defense, which is just what the doctor ordered.

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# Role of the Health Professional in Ending the Tobacco Pandemic: Clinic, Classroom, and Community

**Alan Blum**[1,2]

**ABSTRACT—Physicians and other health professionals have become complacent about the tobacco pandemic, because there is a mistaken belief that the war on smoking has been won. In reality, the survival from lung cancer is little better than it was 30 years ago, and cigarettes have become the most advertised and promoted product in society. The prevalence of overall smoking in the United States has declined by only 0.5%/y during the past decade. Among certain US minority populations, the decline has been far less or nonexistent. Traditional efforts to control the tobacco pandemic have been reactive and static, whereby government agencies, schools, and health professionals provide the public with generic information about the adverse health effects of smoking. As a result of these efforts, it is assumed that individuals will act to change their behavior. In contrast, the tobacco industry is proactive and dynamic, changing its brand-name strategies through advertising and promotion. To more effectively combat tobacco use, health officials need to move beyond patient education and adopt a more active model that includes clinic-based, school-based, and community-based tobacco-control strategies. Use of humorous, satirical images as part of paid counteradvertising campaigns and proactive health education curricula should be part of a concerted effort to end the tobacco pandemic and limit the promotional influence of tobacco companies. [J Natl Cancer Inst Monogr 12:37-43, 1992]**

For health professionals, especially those who work in governmental, academic, or voluntary health agency settings, this discussion may be hazardous to their preconceptions about the smoking pandemic and how to end it. The biggest obstacle to tackling the tobacco problem is complacency—on the part of the public and health professionals alike—stemming from the belief that the war on smoking has been won. Although there is hardly a child or adult who has not heard that smoking is dangerous to health, the fact remains that the prevalence of smoking has declined by only 0.5%/y in the United States during the past decade (*1*). Moreover, women, blue-collar workers, and minority groups in general are not appreciably reducing their cigarette consumption (*2*).

The objective of this article is to challenge health-care professionals to reexamine their approaches, their attitudes, and even their vocabulary to begin examining the tobacco problem as much in terms of promoting a consumerist message of not buying cigarettes as in terms of promulgating a nonsmoking health behavior. This view may lead to a better understanding of why tobacco advertising has been so much more successful than health education and why, in effect, the tobacco companies could be considered leading health educators.

## PROGRESS?

Have we really come a long way? Survival from lung cancer is little better than it was 30 years ago, and cigarettes have become the most advertised and promoted product in society. To accelerate the end of the tobacco pandemic, health professionals must consider that the major preventable cause of death is not lung cancer, heart disease, or smoking; rather, it is Marlboro, which is now the most advertised brand-name consumer product in the world.

Due to the efforts of grass-roots organizations, voluntary health agencies, and progressive governments (eg, Canada, Australia, Norway, and New Zealand), tobacco use is becoming less socially acceptable. Over the past 20 years, all of the major cigarette manufacturers have dropped the word *tobacco* from their names, and smoking has lost its allure for the better educated. Among US doctors, only 1 of 10 still smokes, compared with 2 of 3 in 1950 when the first large studies confirming the link between cigarettes and lung cancer were published (*3*). At the same time, cigarette advertisers, whose livelihoods depend on maintaining the tobacco dependence of hundreds of millions of people worldwide (including several million teenagers each year who start smoking), remain unrestrained. It is an illusion to believe that a major mass-media effort designed to engage the public in a true understanding of the economic and physical toll taken by tobacco use exists in this country. To any adolescent who reads *Sports Illustrated, Rolling Stone, Spin, Playboy, National Lampoon*, or *Mademoiselle* (or who picks up *Time* or *Newsweek* in the school library), the presence of cigarette advertising clearly suggests that smoking is associated with good looks, sexiness, and athletic ability. These appeals to freedom, wealth, and glamour cannot have failed to undermine public health efforts.

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Through ubiquitous social reinforcement of smoking as an attribute of success, the term *antismoking* now has a negative connotation among the poor and uneducated. Notwithstanding tobacco's relationship to between 30% and 40% of all cancer deaths, the mass media (covetous of tobacco advertising revenue) continues to refer to preventive-medicine advocates as "antismoking zealots." The same news corporations would hardly refer to cancer researchers as "anticancer zealots". All who work in cancer treatment, prevention, and research must remind the public at every opportunity that laboratory researchers, clinicians, and preventionists alike are not anti-smoking, but rather anti-cancer, anti-heart disease, and anti-high medical costs.

Unfortunately, too many health professionals still believe that most adverse health behavior can be attributed to peer pressure or poor parental modeling, despite the fact that most peer pressure can be molded through advertising propaganda. In the United States, one of the most ubiquitous current cigarette advertising campaigns features a camel cartoon character. Coincidentally, this brand is catching up to Marlboro as the most popular cigarette among adolescents. Is this peer pressure? Lest we think that an advertising ban will remove these influences, consider the use of movies such as *Superman*, seen by tens of millions of teenagers worldwide, which contains dozens of images of the Marlboro cigarette logo in several scenes (*4*), or *Days of Thunder*, with its many shots of Winston cigarette logos on racing cars.

More than $3 billion is now spent each year in the United States alone to promote cigarette smoking (*5*). Despite the vaunted claims of tobacco executives that cigarette advertising is aimed solely at enticing the confirmed adult user to switch brands—and never at adolescents—it is irrefutable that every advertisement for cigarettes represents an encouragement to smoke and a reinforcement of the social acceptability of smoking.

Tobacco companies, individually and collectively as the Council for Tobacco Research, continue to provide funding to medical schools for smoking-related research, as if to imply that more research is really necessary to settle what the industry calls the smoking and health "controversy." Such funding is often commingled with government grants. The tobacco industry also publicizes its funding of nontobacco research and various health charities, with the possible aim of enhancing its image.

Nowhere has the tobacco industry been more successful in creating a positive association with cigarettes than through sports sponsorship. Even from the onset of the ban on television cigarette promotion in 1971, tobacco brand-name sponsorship of televised sporting events became a more effective vehicle than overt cigarette advertising for reaching young viewers. Techniques such as placing billboards advertising cigarettes in baseball stadiums at locations frequently focused on by the television cameras and using tobacco brand-name logos on racing cars and drivers' uniforms have effectively undermined the intent of the broadcast ban on tobacco promotion, not to mention the low-budget antismoking education efforts of government health agencies and voluntary organizations.

Smoking thus continues to go unrecognized by the public as the leading cause of preventable health problems, largely because cigarettes are the most heavily advertised US product. This advertising not only recruits new users but also buys the complacency of those who do not smoke. The tobacco pandemic is not a static concept, whereby information about adverse health effects is given on which individuals will act to change their behavior; rather, it is a dynamic concept, whereby the tobacco industry changes its strategies much like the AIDS virus alters its antigenic coat to outsmart the challenges of the host organism. The tobacco industry is a vibrant and dynamic force that researchers must monitor as they would a parasitic disease.

For example, as the consumption of cigarettes very slowly declines in the United States, American companies are dramatically expanding their markets in eastern Europe, Asia, Africa, and Central and South America. Thus, although public health organizations have long criticized government price supports for tobacco, comparatively little clamor has been raised toward ending US exports of cigarettes. Similarly, a disproportionate allocation of resources and personnel for smoking-cessation programs for adults by public health agencies and voluntary health organizations may have come at the expense of a concerted mass-media primary-prevention effort designed for young people.

## TRAGEDY OF ETHNIC MARKETING

The age-old problems caused by tobacco in US society are dramatically worse in minority communities. The fact that cigarette smoking has become less fashionable among upper- and middle-income groups over the last decade may have lulled the public into believing that the United States is on its way to reducing the enormous toll taken by smoking. As the Task Force on Black and Minority Health of the Department of Health and Human Services pointed out in its 1985 report (*6*), there are substantial inequities in the health status of US ethnic and minority groups. The report noted that there are 58 000 excess deaths each year among black Americans compared with the death rate for the white population. Principal among the rising preventable causes of death are cardiovascular disease and lung cancer, the two major consequences of smoking (*6*). Blacks and Hispanics have the highest rates of these diseases in the US population, a fact that is obscured by a tendency in medicine to focus attention on the rare but highly publicized diseases that are more common in blacks than in others, eg, sickle-cell anemia (*7*). However, fewer than 300 of the 58 000 excess deaths among blacks each year are due to sickle-cell anemia and related blood conditions, a small fraction compared with the number of deaths attributable to smoking.

Those with the least income are spending the most on cigarettes—more than $700/y to maintain a pack-a-day

habit. There is a constant presence of tobacco advertising on the news, sports, fashion, and life-style pages of newspapers and other publications directed at US blacks and Latinos. Tobacco companies have also become the major benefactors of black and Latino organizations, most of which continue to remain silent on the problem of tobacco use and promotion.

In many ethnic neighborhoods, as much as 80%–90% of all billboard advertising is for brands of tobacco and alcohol products (*8*). In black communities especially, cigarette advertising is the single common theme in various retail outlets from food stores and supermarkets to beauty parlors and barbershops (as well as dry cleaners, laundromats, gas stations, and bars and grills). Mass-transit systems, relied on more by lower-income commuters than by others, are an increasing showcase for cigarette advertising.

Because of their lower literacy rate, newer immigrant groups depend on television as their prime medium of communication and information. Taking advantage of this, tobacco companies have made an end run around the Public Health Cigarette Smoking Act of 1969 by getting cigarette brand names on various cultural and sporting events. Ironically, money-saving offers represent a major appeal by the tobacco industry to people with the lowest disposable income. There has been a dramatic increase in the number of rebate coupons in magazines and newspapers, good for substantial discounts on cartons of cigarettes. The free distribution of sample packs is also especially common in inner-city communities. The fact that a pack-a-day smoker will spend more than $7000 in 10 years on cigarettes is not highlighted in tobacco company advertising.

The tobacco industry had been especially adept at exploiting racial identity in defining a profitable market among ethnic minorities. R.J. Reynolds sponsors Camel street fairs in Latino neighborhoods. Brown and Williamson presents annual Kool Achiever awards to people who have improved the "quality of life in inner-city communities"; the tobacco company has even enlisted the National Urban League, the National Newspaper Publishers Association, and the NAACP in the nominating process. During Black History Month each February, R.J. Reynolds has featured discount coupons in black-oriented magazines for various brands of cigarettes, complete with pictures of scientists such as George Washington Carver.

Publishers of newspapers and magazines with predominantly black readership who accept tobacco advertising are not reluctant, disinterested, or passive recipients of revenue from advertising that is intended to promote the use of a legal product in a free society. To the contrary, like their counterparts at *Time* and *Newsweek*, publishers of the minority-oriented press aggressively court tobacco advertisers by emphasizing their credibility and their reach in the community they purport to serve.

## OFFICE-BASED STRATEGIES

Although many people say they have simply stopped smoking on their own, these individuals may not consciously attribute their success to the increasing social pressures that reinforce their decision. Not only has organized medicine become united in the past few years on the need for more assertive office-based and community-wide strategies to end smoking, but other forces in society (eg, large corporations and government agencies) have also implemented smoke-free policies. The success of smoking-cessation programs for individual patients is likely to be dramatically enhanced in the presence of both workplace smoking bans and multimedia counteradvertising strategies that weaken the influence of the tobacco industry and reinforce the physician's office-based efforts.

Ideally, the validity of the success rate of a smoking-cessation method should rest on the results of a controlled double-blind study for which there is follow-up of at least 6 months' duration for all participating subjects. Few published outcome evaluations meet such criteria. Despite insufficient evidence to confirm advertising claims, expensive commercial aids and clinics for smoking cessation proliferate. Promotions for various pharmacological agents, mail-order gadgets, and clinics in smoking cessation reinforce the notion that cigarette smoking is primarily a medical problem with a simple, prescribable, nonindividualized solution. When a patient requests a "drug that will help me stop smoking," the physician must confront the dilemma of not wanting to dash the patient's expectation while emphasizing that a drug or device is, at best, an adjunct and not a means of smoking cessation.

The physician's active involvement in smoking cessation, similar to his or her role in the prevention of smoking among teenagers and children, can be crucial. More than a decade ago, when efforts to discourage smoking were much less widespread and accepted, Russell et al. (*9*) found that 1–2 minutes of simple but unequivocal advice to stop smoking on the part of the physician resulted in a cessation rate of over 5% measured at 1 year, versus only 0.3% in the control group.

Many factors may inhibit physician involvement in smoking cessation, eg, perceived or real lack of time, lack of reimbursement by third-party payers for such counseling, and lack of peer-group reinforcements in a technologically oriented, tertiary-care–centered health system. There is much the physician can do to become a better teacher in lieu of relegating this role to ancillary personnel or a smoking-cessation clinic or by handing the patient a pamphlet off the shelf. The physician can develop an innovative strategy beginning outside the hospital, clinic, or research center. A bus bench, billboard, or sign in the parking lot with a straightforward or humorous health-promotion message helps establish a thought-provoking and favorable image. In the waiting area, removal of ashtrays and the placement of signs noting that "in the interest of comfort, safety, and health, this is a smoke-free environment" further reinforce the message. Magazines with cigarette advertisements should not appear in the physician's office in the absence of prominent stickers or rubber-stamped messages calling patients' attention to the deceptive, absurd nature of this advertising. Physicians'

commitment to preventing their offices from becoming vehicles for cigarette sales would make a substantial contribution to health promotion.

The key to successful smoking-cessation efforts is a positive approach. A discussion about the diseases caused by smoking and the harmful constituents of tobacco smoke is essential, but the benefits of not smoking must be emphasized at least as strongly. Educating patients solely about the facts of smoking in a single office visit is unlikely to result in behavioral change. On the other hand, the physician can, by using creative analogies related to the patient's occupation, hobbies, or romantic interest, succeed in changing the patient's attitude toward smoking.

A revocabularization on the part of the physician is essential for making progress in office-based smoking cessation. Instead of *pack-year history*, a more relevant term is *inhalation count*. A patient who smokes one pack/d will inhale more than 1 million doses of cyanide, ammonia, carcinogens, and carbon monoxide in less than 15 years, not including the effects of inhaling other people's smoke. Another way to emphasize the enormous amount smoked is in financial terms: a pack-a-day cigarette buyer will spend in excess of $700/y (calculated at approximately $2.00/pack), which is in excess of $8000/decade had that money been placed into a savings account or bond. One could also allude to the joyful feeling of finding a $50 bill every few weeks—the amount that a smoker would save had the money not been spent on cigarettes. One patient who began smoking in the Marines at the age of 18 years, and who still smoked three packs/d at 33 years of age, ruefully remarked that he had "smoked a Porsche."

Because patient education in general and smoking cessation in particular depend on the knowledge of both physician and patient of the deleterious aspects of adverse health behavior, the cognitive component alone is insufficient. Both physician and patient must be motivated to succeed.

The three keys to office-based smoking cessation are to personalize, individualize, and demythologize. The physician can learn to personalize approaches to smoking cessation by carefully screening the pamphlets and other audiovisual aids available in the office. It is essential to scrutinize all office materials in the way that a new drug or medical device would be evaluated. Personally handing a brochure to the patient while pointing out and underlining certain passages or illustrations will provide an important reinforcing message. Pamphlets, posters, and signs should be changed or updated frequently.

Individualizing the message to the patient is the cornerstone of success in patient education. The same cigarette counseling method cannot be used for a high school girl, a construction worker, and an executive already showing signs or symptoms of heart disease. In the case of a high school girl, the physician should not focus on abstract concepts (eg, emphysema and lung cancer) but rather the cosmetic unattractiveness of yellow teeth and bad breath, the loss of athletic ability, and the financial drain that results from buying cigarettes. For the male construction worker, the physician might suggest the likelihood of fewer lost paydays, greater physical strength, and the possibility of a lengthier sex life were he to stop smoking cigarettes.

In the case of the concerned executive, it is especially important to demythologize certain beliefs about smoking, such as that the low-tar cigarettes are safer. The use of so-called low-tar brands, which should be referred to as "low poison" by the physician, may in fact result in compensatory deeper inhalation of greater concentrations of chemical additives and noxious gases that increase heart attack risk. One way to highlight the absurdity of the belief that low-tar cigarettes are safer is to ask rhetorically, "Safer than what, fresh air?" or to wonder aloud if it is safer to jump from the 90th story of the Empire State Building instead of from the roof. Another analogy is to point out that a person would never think of buying a loaf of bread, or any other consumer product, that was advertised as containing "only 2 mg of cancer causers." Counseling should call attention not only to the inevitable risks of smoking cigarettes but also to the chemically adulterated tobacco product itself, its inflated price, and the ubiquitous and ludicrous ways in which brands are promoted.

## COMBATING COMMON MYTHS

The saddest myth about smoking is that it relieves stress, which can be debunked by pointing out that the stress that is relieved is that resulting from cigarette dependence; this is the essence of addiction. The second saddest myth, reinforced in advertisements for Virginia Slims and a host of new lines of thin cigarettes intended for women and girls, is that smoking can keep them from gaining weight. Aside from calling attention to the many obese women who smoke and attempting to correct the misapprehension that being overweight is a greater health risk than smoking, the physician can point out that smoking inhibits appetite by damaging the taste buds and other digestive tract cells. Smoking also results in more sedentary behavior through loss of lung capacity and cardiovascular fitness. Weight gain does not have to accompany smoking cessation if patients relearn to enjoy walking and running; in short, by no means will all people who stop smoking gain weight. Even among those who do, the average weight gain is less than 5 lb (*10*). Moreover, the slightly lower weight of many who continue to smoke is associated with a higher-risk body fat distribution.

From the physician's standpoint, perhaps the biggest myth that has been encouraged in the medical literature is that the patient must be "ready to quit." Although common sense dictates that those who express a greater interest in smoking cessation will have a greater success rate, patients who do not express an interest in stopping smoking symbolize the overall challenge that physicians face in curbing this pandemic. One reason for the lack of patient motivation may be a sense of inevitability of failure. It is conceivable that, by not educating the unmotivated smoking patient, the physician is in effect reinforcing the myth

that it may be too difficult to stop smoking. Setting a "quit date," the sine qua non of the smoking-cessation literature, may rationalize the continuation of an adverse health practice and may strengthen denial. In other words, it is helpful to remind patients that they can stop immediately.

## CONSUMER ADVOCACY ROLE

Traditional office-based approaches begin by asking the patient if he or she smokes, how much he or she smokes, and when he or she started smoking. Although this may provide the physician with relevant data for charting purposes, this approach is too often a signal for the patient to become defensive and resistant to further discussion, especially if he or she has no intention of stopping smoking. There are, however, alternative ways of obtaining information while piquing the patient's interest in the subject. By using and identifying with the vocabulary used by the cigarette consumer, the physician can adopt (and be perceived in) the role of consumer advocate, as opposed to medical finger wagger. The most important and nonthreatening questions to ask are about the brands that are bought and how much is spent on cigarettes. Patients are likely to be surprised and intrigued by these apparently nonjudgmental questions, which can be asked at any time in the course of the interview. These questions suggest that the physician is not solely a know-it-all and a preacher on the dangers of tobacco use. In effect, a question about the cost of cigarettes shows concern for the patient's financial well-being. Inquiring as specifically as possible about the brand name, style, length, and package design—for example, Marlboro/Menthol/Lights/100s/box— will lead to a greater physician understanding of the same vocabulary used by the person who buys cigarettes, thus narrowing the communication gap. The patient may even begin to laugh aloud at the foolishness of this vocabulary, especially when he or she is encouraged to show the physician the package and to appreciate how little information about the product appears beyond the attractive design.

## BEYOND THE EXAMINING ROOM

What specific measures can be used in planning strategies for preventing and ending the use and promotion of tobacco beyond the clinic? Foremost, there must be additional research, only a small part of which should be directed toward studying health habits, smoking-related disease incidence, and attitudes toward smoking. Health advocates must take the lead from tobacco companies and other purveyors of unhealthy products who have sought to overcome the burden of evidence of scientific research. A great deal can be learned by studying the techniques of the tobacco industry, which are in sharp contrast to those of health agencies. Health professionals need to conduct far more consumer research (eg, face-to-face surveys and in-store observations of buying habits) in lieu of health-behavior surveys.

To this end, school-based programs must be made more engaging (and enraging), placing an equal emphasis on what could be called the "three Ps": peer pressure, parental modeling, and propaganda. Curriculum designers for secondary schools should use a simple formula of fear, humor, and anger. Too few educational programs in or out of the classroom (especially in primary schools) go beyond scare tactics and cognitive objectives about the dangers of smoking. By analyzing and satirizing the promotional techniques of tobacco companies and their media allies, students can delight in turning the tables on the firms that create cigarette advertisements. In studying the long arm of the tobacco industry around the world and making the connection between tobacco advertising and the deaths of family members and friends from tobacco-related diseases, students may learn to redirect their anger from teachers, parents, and health professionals to the authority figures in society who attempt to promote unhealthy products to children.

Because the onus for ridding society of tobacco and its promotion should not rest solely on parents, teachers, and health-care officials, reinforcement strategies must be created in health-care settings, religious and civic organizations, cultural and sports arenas, and the mass media. Health-care authorities and legal scholars have an ideal opportunity to combine forces in litigation by suing those who make and promote tobacco products. This includes seeking redress on behalf of those killed or injured in fires caused by cigarettes, which are designed to keep burning even when unattended.

The existing regional, national, and international coalitions to carry out a multilevel strategy toward ending the cigarette smoking pandemic are regrettably few. The necessary steps are not unidimensional; rather, they are multifocal and require concurrent strategies. Paid counteradvertising that ridicules specific tobacco brand names and advertising images is the most important force that will result in reduced consumption. So-called public service advertising space donated by media corporations to health agencies and other nonprofit groups is weak, bland, ineffectual, and seldom seen, because it is in effect controlled by the media. An excise tax dedicated solely to the purchase of counteradvertising space would be ideal, but this investment must be made even without such tax support.

In its only meaningful national test (between 1967 and 1970, when anticigarette commercials were shown 1500 times/y on television), counteradvertising had a greater effect in reducing smoking than the more frequently shown cigarette advertisements had in increasing cigarette sales. In the absence of memorable paid counteradvertising, the tobacco industry continues to run the year-round political-style campaign of an incumbent, with virtually no planned exposure by the opposition.

For health-promotion efforts to succeed by the year 2000, it will be essential to focus on the cigarette industry rather than on the behavior of individual cigarette smokers.

A ban on tobacco advertising and promotion is another ideal but lacks sufficient support from Congress and the president. On the other hand, enforcement by the US attorney general of existing laws that regulate tobacco advertising could be a major step forward. For example, the Public Health Cigarette Smoking Act of 1969, which prohibits the promotion of cigarette brands on television, calls for a $10 000 fine for each violation of the law. If this law could be applied to national telecasts of completely tobacco-sponsored sporting events, levying fines of tens of millions of dollars per event (based on the hundreds of tobacco brand names shown on television during a tennis match or auto race), neither media corporations nor tobacco companies could afford to continue televising tobacco-sponsored sporting events.

As for the sports events themselves, cigarette sponsorships must be challenged not solely by attracting nontobacco sponsors but also by the frequent ridiculing of existing tobacco sponsors as a way of reinforcing the absurdity of associating smoking and athletic performance. A national organization, Doctors Ought to Care (DOC), was founded in 1977 to focus attention on the promotion of unhealthy products. By lampooning brand names as part of paid counteradvertising and sponsoring antismoking events, DOC has been instrumental in pointing out the vulnerability of the tobacco industry. Since 1978, DOC has used its version of the Virginia Slims Tennis Tournament—the Emphysema Slims, with the slogan "You've coughed up long enough, baby"—to counter cigarette advertising. DOC convinced the 1988 US boomerang team, which was about to compete in the world championships in Australia with sponsorship money from Philip Morris Tobacco Company, to accept its sponsorship instead, complete with a uniform that featured the international nonsmoking symbol. For $9000, DOC sent the team to Australia, where they won the world boomerang championship; afterward, many sportswriters cited DOC's effort as a model for future sports sponsorship by health organizations.

The passage of smoke-free indoor legislation has been the single major advance in this country in terms of reducing cigarette consumption, thanks to the efforts of activist nonsmokers' rights groups. Unfortunately, black and Hispanic membership in these organization is small, and the success of tobacco companies in influencing minority group lawmakers has been a major disgrace.

There is great need for a no-holds-barred revocabularization, ie, a new set of terms, images, and other symbols with which to communicate to the public about tobacco products and manufacturers. A crucial phase in US public health will be reached when the seven major tobacco companies in the United States are recognized as cancer's seven warning signs: Philip Morris (makers of Marlboro and Virginia Slims), RJR/Nabisco (R.J. Reynolds Tobacco Company: Winston, Salem, and Camel), Loews (Newport and Kent), Brown and Williamson (Kool and Barclay), American Brands (Carlton and Lucky Strike), Liggett and Meyers (generics), and UST (United States Tobacco Company: Skoal Bandits and Copenhagen spitting tobaccos). Nor should it be underestimated that these are indeed primarily tobacco companies: although cigarette sales now account for approximately half the revenues of Philip Morris and RJR/Nabisco, they provide more than 70% of their profits.

To traditional public health workers, hard-hitting satirical counteradvertising that shifts public focus away from the substance (tobacco), the user (smoker), and the effects of the use of the substance (lung cancer) to the manufactured product, the way in which it is promoted, and the promoters may seem overly cynical and appears to risk incurring the wrath of the tobacco industry and its allies. This is precisely the intention. Cigarette sales have not been seriously damaged by warnings of the dangers of smoking, because danger has become part of the formula for selling cigarettes, especially to the fearless adolescent. Tobacco companies have successfully responded to thousands of research reports describing the dangers of smoking by funding hundreds more to seek further proof. However, although the health consequences may not be a deterrent, ridicule by consumers of the product, its promotion, and its promoters holds great potential for hurting cigarette profits.

A concerted effort that includes researchers, physicians, nurses, dentists, pharmacists, and all other health professionals is essential for ending the tobacco pandemic. All responsible citizens, health organizations, and corporations must be part of this effort to limit the promotional influence of tobacco companies.

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# Projecting International Lung Cancer Mortality Rates: First Approximations With Tobacco-Consumption Data[1]

John P. Pierce, Leigh Thurmond, *and* Bradley Rosbrook[2,3]

**ABSTRACT—Cigarette smoking is strongly associated with later lung cancer; British data show a 0.83 correlation between tobacco consumption and lung cancer mortality 21 years later. We apply a simple tobacco-consumption model to data from countries in the Organization for Economic Cooperation and Development (OECD) to test the model in some nations and to roughly estimate future rates in others. This analysis provides some indication of the usefulness of the model, which could be applied to predictions for countries in which data are limited. This model predicts a US decline in male lung cancer mortality of approximately 25% by 2005 (a plausible prediction given recent declines in birth-cohort-specific lung cancer mortality rates); it also predicts reasonably well the start of documented declines in lung cancer mortality. According to this admittedly simple model, lung cancer mortality rates will increase in most European countries and Japan until 2000, but the twenty-first-century lung cancer epidemic will mostly occur in Asia. [J Natl Cancer Inst Monogr 12:45-49, 1992]**

Lung cancer has been a twentieth-century epidemic in developed countries. In the United States, for example, lung cancer mortality made up only 1.5% of all deaths in 1950. Since then, it has become an increasingly more frequent cause of death, and in 1987, 7.4% of all deaths were caused by lung cancer. A similar pattern of increase has occurred in almost all Western countries. In the past, lung cancer has been a disease confined mainly to men, and the pattern of tobacco use over time has been quite different for women; therefore, we confine our analysis to the prediction of lung cancer mortality rates in men.

Treatment is unlikely to result in an improvement in mortality rates; less than 20% of lung cancers are detected at a localized stage, and the 5-year survival rate is still approximately 13% (*1*). However, lung cancer would appear to be almost completely preventable. Although lung cancer occurs in those who have never smoked, it is rare: the rate is less than 20/100 000 in the United States (*2*). Furthermore, even this rate is inflated because it does not consider exposure to passive smoking (*3*). Incontrovertible data have shown that cigarette smoking is the major cause of lung cancer: 90% of all lung cancers in men in the United States are directly attributable to cigarette smoking (*2*).

## BACKGROUND FOR TOBACCO-CONSUMPTION MODEL

### Correlation Between Tobacco Consumption and Lung Cancer Mortality

Using cigarette sales data (by weight) from the United Kingdom collected from 1889 to 1942 and lung cancer mortality data from 1889 to 1982, Peace (*4*) identified that the correlation between these factors was maximized at 0.83 with a 21-year lag time. In another study of 10 countries, Doll (*5*) reported a good correlation (0.73) between cigarette consumption in 1930 and the development of lung cancer 20 years later. When Doll and Peto (*6*) repeated this analysis for 21 countries (using 1950 consumption of manufactured cigarettes and 1970 lung cancer mortality rates for 35- to 44-year-old men), they obtained a similar correlation. When we analyzed tobacco consumption data for 1966 (*7*) and lung cancer mortality rates for 12 countries from 1985 to 1986 (*8*), we found a correlation of 0.55 (fig. 1).

### Tobacco-Consumption-Based Model Versus Other Models for Forecasting Lung Cancer Mortality Rates

Sophisticated models of lung cancer mortality rates have been developed by Doll and Peto (*9*), Stevens and Moolgavkar (*10*), and Moolgavkar et al. (*11*) using data from the British Physicians Study. The Doll and Peto model has been shown to be represented reasonably well by the British lung cancer data (*12*). However, in many developing countries, no one collects the detailed data required for such models (eg, distributions of duration of smoking or the number and type of cigarettes smoked).

Therefore, we present a simple model based on tobacco-consumption data that can be used to provide broad estimates that will indicate the most likely directions of lung cancer mortality rates for other countries. This model cannot predict rates with the accuracy of more sophisticated models, but it can provide the first approximations that may help guide public-health decisions, especially in countries for which detailed data are not available.

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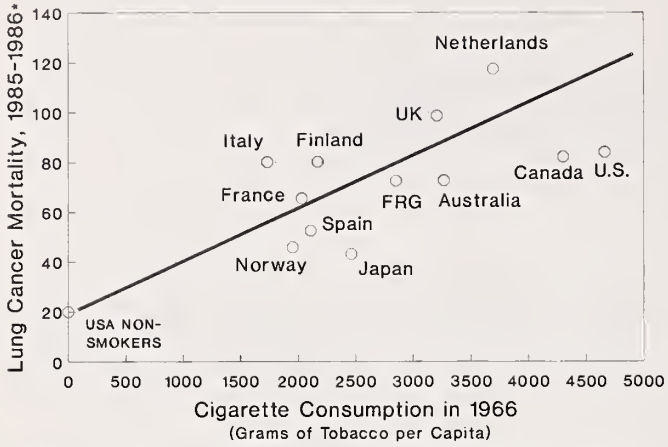


**Figure 1.**—Lung cancer mortality rates in 1986 for different OECD countries are plotted according to their tobacco-consumption levels in 1966. Ordinary least squares are used to plot line of best fit. *Deaths per 100 000. From (*8*, *16*).

One limitation of the simple model is that it tends not to project trends accurately when the tobacco-consumption curve is flat (as discussed below). Also, the projections based on this approach would probably be more accurate if cigarette-consumption data were available separately from tobacco-consumption data. However, in developing countries (for which more accurate prediction methods cannot be used because of lack of data), this simple model may be used as an alternative to not attempting any predictions at all.

The value of these projections depends on whether this tobacco-consumption model for lung cancer will provide estimates that are at least close in accuracy to estimates provided by the more sophisticated models. This has been assessed by looking at the US data.

Brown and Kessler (*13*) have developed a sophisticated model of lung cancer mortality rates using the best estimates available of exposure to tobacco smoke in the population. Their projection predicts an 11% decline in lung cancer in men by 2005. Our simple tobacco-consumption projection suggests that the decline in lung cancer in men will be approximately 25% by 2005.

The Brown and Kessler model (*13*) was developed with lung cancer mortality data through 1982. Lung cancer mortality data by birth cohorts are now available through 1986 (*14*). Recognizing that smoking behavior is rarely initiated after the age of 25 years (*2*) and that, in men, the attributable risk of lung cancer from smoking is 90% (*2*), declines in lung cancer mortality rates within the birth cohort can be assumed to be maintained as the birth cohort ages. In white men between 35 and 44 years of age, lung cancer declined by 28.7% between the periods 1973–1976 and 1983–1986 (*14*). Assuming that this rate of decline continues to be lower throughout their life span and that of younger birth cohorts, the overall lung cancer mortality in men in the United States will decline by as much as 18% within the next 20 years. This estimate lies between the projections from the Brown and Kessler model (*13*) and the tobacco-consumption model. Accordingly, we believe that the tobacco-consumption model has some utility in projecting future lung cancer mortality rates, especially in countries that do not have the detailed smoking-exposure data available in the United States and the United Kingdom.

## TESTING TOBACCO-CONSUMPTION MODEL IN ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD) COUNTRIES

### Tobacco Consumption

Many countries levy an excise tax on tobacco that is collected at the wholesale level. From accurate statistics available from this excise tax data, tobacco consumption can be estimated. Total tobacco consumption is used for comparative purposes because data from different countries vary considerably in the amount of total tobacco consumption attributable to the use of manufactured cigarettes. Total tobacco-consumption figures were obtained from excise tax data published for countries participating in the OECD, which used weight in grams of each tobacco product consumed (a cigarette contains ~1 g of tobacco). These data were divided by the estimated population over the age of 15 years to obtain an estimated per-capita consumption level. Also, the year of peak tobacco consumption for each country was important for our analyses, because this information should help estimate the year of peak lung cancer mortality rate in the different countries.

Figure 2 presents the tobacco-consumption data for the five English-speaking OECD countries (Australia, Canada, New Zealand, the United Kingdom, and the United States). Although per-capita consumption levels are historically higher in the United States and Canada than in the other OECD countries, all countries reported a sharp decline in tobacco consumption from at least the mid-1970s. Per-capita consumption appears to have peaked in the United States around 1964, in Australia around 1969, in the United Kingdom around 1972, in New Zealand around 1975, and in Canada around 1981.

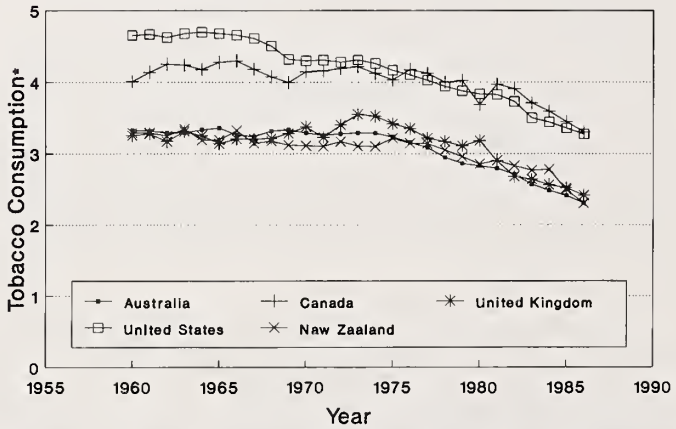


**Figure 2.**—Tobacco consumption from 1960 through 1985 in Australia, Canada, New Zealand, the United Kingdom, and the United States. *Thousands of grams per capita. From (*7*).

Although the peak consumption in these countries occurred at different times, the decline from that peak to the 1986 level was similar in the United States (30%), Australia (31%), and the United Kindgom (29%); the decline was slightly lower in Canada (23%).

Data on per-capita consumption of tobacco show that the consumption level in Finland, Norway, and Sweden has been considerably lower than in the English-speaking OECD countries (fig. 3). Tobacco consumption has not risen in any of these countries since the mid-1970s. Although smoking has declined in Finland since 1974, in Norway since 1969, and in Sweden since 1976, the rates of decline are considerably lower than in the English-speaking countries (~10% reductions from peak in both Norway and Sweden and a 19% reduction in Finland). Between 1960 and 1969, tobacco consumption in Norway increased by an average of 34.1 g per capita/year ($r$ = 0.76).

The tobacco-consumption data for France, Italy, and the Federal Republic of Germany (FRG) are presented in figure 4. Tobacco consumption peaked in France later (1985) than in either FRG (1972) or Italy (1982). In each case, the peak consumption was considerably lower than in the English-speaking OECD countries. The decline from the peak to 1986 was 13% in FRG, 4% in France, and 6% in Italy. From 1960 to 1985, consumption in France increased by an average of 20 g per capita/year ($r$ = 0.94); in Italy, consumption increased at an average of 39 g/year from 1960 to 1982 ($r$ = 0.98).

As shown in figure 5, tobacco consumption in Japan peaked in 1975 at a level similar to that in the United Kingdom and Australia (fig. 2). Between 1960 and 1975 in Japan, per-capita consumption increased by a rapid average of 100 g/year in Japan ($r$ = 0.99). Then, in the 12 years from the peak to 1986, consumption in Japan declined slightly (3%). Consumption levels in Spain and Greece may have peaked in 1985 (fig. 5): from 1960 through 1985, those levels increased by averages of 54 g/year in Spain ($r$ = 0.95) and 68 g/year in Greece ($r$ = 0.92).

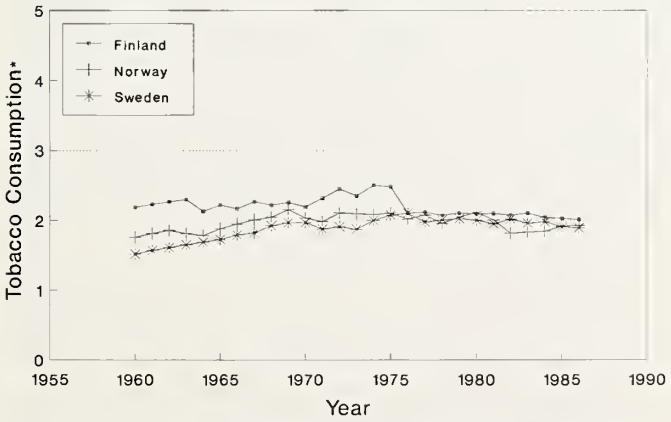


**Figure 3.**—Tobacco consumption from 1960 through 1985 in Finland, Norway, and Sweden. *Thousands of grams per capita. From (7).

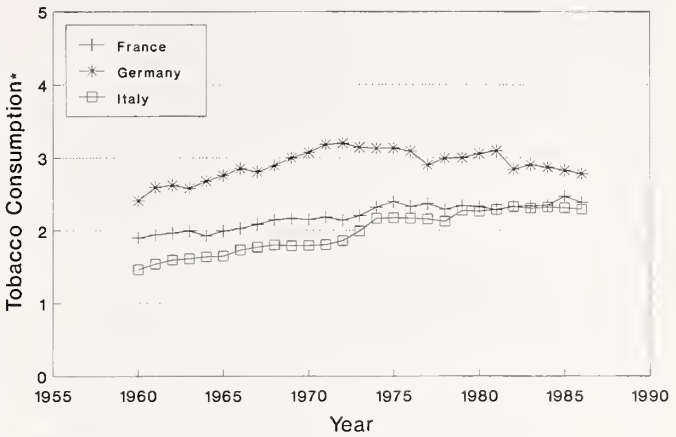


**Figure 4.**—Tobacco consumption from 1960 through 1985 in France, Germany, and Italy. *Thousands of grams per capita. From (7).

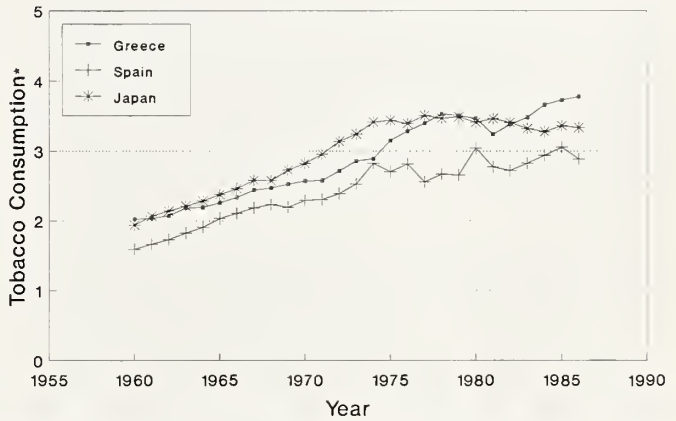


**Figure 5.**—Tobacco consumption from 1960 through 1985 in Greece, Japan, and Spain. *Thousands of grams per capita. From (7).

Figure 6 shows the per-capita tobacco consumption for the Netherlands, Belgium, and Denmark. Among these countries, the first to experience a peak in consumption was Denmark (1973), followed by the Netherlands in 1979 and by Belgium in 1983. The peak consumption levels in these countries are similar to those in the English-speaking countries. From peak consumption year to 1986, consumption declined by 30% in the Netherlands, 17% in Denmark, and 11% in Belgium. The rate of increase in consumption between 1960 and the peak year averaged 45 g/year in the Netherlands ($r$ = 0.81) and 21 g/year in Belgium ($r$ = 0.69); tobacco consumption did not change significantly in Denmark ($r$ = 0.28).

### Predicting Lung Cancer Mortality Rates via Tobacco-Consumption Model

We use a simple tobacco-consumption model to predict the year in which lung cancer mortality rates in men will peak in various countries and to estimate the probable lung cancer mortality rate in that peak year. We predict changes in lung cancer mortality rates on the basis of

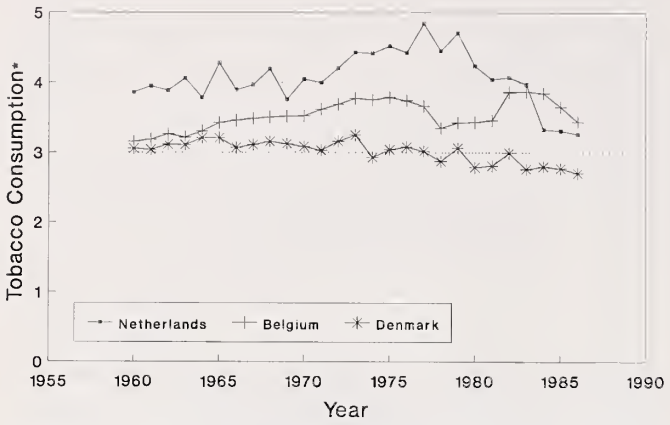


**Figure 6.**—Tobacco consumption from 1960 through 1985 in Belgium, Denmark, and The Netherlands. *Thousands of grams per capita. From (*7*).

declines in tobacco consumption (which, in the Western countries for which data are available, have resulted from declines in male smoking prevalence) (*15*, *16*). To estimate the peak year for lung cancer mortality rates, we simply add 20 years to the peak year of tobacco consumption. The validity of this simplified calculation can be tested with the countries in which tobacco consumption peaked in the 1960s.

Table 1 presents the lung cancer mortality data for 1975 through 1986 for Australia, Canada, New Zealand, and the United States and the predicted peak year for each country based on the simple tobacco-consumption model. From this model, lung cancer mortality rates in Australia, Canada, and New Zealand were predicted to have peaked between 1985 and 1989. The observed lung cancer mortality rates appear to have peaked in Australia and New Zealand in the period before this (1980–1985), and the rate in Canada appears to have been close to peaking in 1986. In the United States, the predicted peak was 1984, and the rate appears to have been close to peaking in 1986.

In one group of countries (the United Kingdom, Finland, Sweden, and FRG), the lung cancer mortality rates peaked earlier than predicted by the simple tobacco-consumption model (table 1). The rate for the United Kingdom was predicted to peak in 1992, but the actual rate peaked more than 10 years earlier; by 1986, the lung cancer mortality rate had declined by 9% from the peak. In Finland, lung cancer mortality rates appear to have peaked in the late 1970s (rather than in 1994 as predicted); by 1986, the rate was 17.6% lower than the peak rate. In Sweden, lung cancer mortality rates peaked in the late 1970s (long before the predicted 1996) and had declined by 8% by 1986. Lung cancer mortality rates in FRG also appear to have peaked in the early 1980s rather than in 1992 as predicted.

These data show that our simple model failed to predict the year of downturn of lung cancer mortality rates in men in these four countries. This failure may be an artifact of the tobacco-consumption data rather than a major problem with the model itself. Whereas tobacco consumption

**Table 1.**—Countries in which lung cancer mortality rates in men have peaked

| Country | Predicted peak year | Actual lung cancer mortality rates per 100 000 | | |
|---|---|---|---|---|
| | | 1975–1979 | 1980–1985 | 1985–1986 |
| Australia | 1989 | 70.1 | 72.5 | 72.2 |
| Canada | 1986 | 73.3 | 81.6 | 82.2 |
| New Zealand | 1986 | 74.2 | 75.2 | 69.4 |
| United States | 1984 | 78.3 | 83.3 | 84.1 |
| United Kingdom | 1992 | 108.6 | 102.3 | 98.8 |
| FRG | 1992 | 72.2 | 73.5 | 72.6 |
| Finland | 1994 | 97.3 | 92.3 | 80.2 |
| Sweden | 1996 | 38.0 | 36.5 | 35.0 |

From (*6*).

in the United Kingdom peaked in 1972 (fig. 2), the consumption curve was flat from the start of the 1960s, except for a small surge in the early 1970s. The curve for tobacco consumption in Finland was also flat through the 1960s (again, a small surge in consumption was reported in the early 1970s) (fig. 3). In FRG (fig. 4) and Sweden (fig. 3), this was not the case: consumption in both countries clearly increased throughout the 1960s. (An anomaly may be present in the Swedish data because some tobacco users changed from cigarettes to snuff use [*15*], and snuff has a much lower lung cancer risk.) These discrepancies serve as further reminders that the correlation model used in this study is much simpler than the true relationship between lung cancer and tobacco use; therefore, the method is appropriate for use only when the data available do not allow use of other, more sophisticated models.

The predicted peak lung cancer rate in men for each country was estimated as follows. First, we determined the slope of the tobacco-consumption data for the 20-year period before the year of peak consumption. Next, we adjusted this rate by the ratio of the slope of the lung cancer mortality rates from 1975 to 1985 to the slope of the tobacco-consumption data for 1960–1965, the only data available for the period approximately 20 years earlier. Finally, we multiplied this adjusted rate by the number of years from 1985 to the expected peak year and added the result to the lung cancer mortality rate for 1985.

Table 2 presents the projections for peak lung cancer mortality for countries that have not yet reached their maximum levels; in each of these countries, tobacco consumption had reached its peak within the last 20 years. The simple tobacco-consumption model predicts that lung cancer mortality rates in Denmark, Japan, Norway, and the Netherlands will peak before the turn of the century. The peak in Denmark is not expected to be much higher than the 1986 rate; however, the rate in Japan is predicted to increase by approximately 35% over the 1986 rate before the peak is reached in 1995. Lung cancer mortality rates in Belgium, France, Italy, and Spain are expected to peak between 2002 and 2005. In Belgium, the rate should increase by another 8% from the level reached in the early

**Table 2.**—Future trends in lung cancer in men in countries in which mortality has not peaked

| Country | Male lung cancer mortality rates per 100 000 | | | Expected peak rate* (year) |
|---|---|---|---|---|
| | 1975–1979 | 1980–1984 | 1985–1986 | |
| Belgium | 108.7 | 117.7 | —† | 127.0 (2005) |
| Denmark | 72.8 | 80.9 | 81.1 | 81.4 (1993) |
| France | 57.1 | 62.9 | 65.5 | 98.5 (2005) |
| Italy | 68.1 | 80.1 | —† | 122.1 (2002) |
| Japan | 32.7 | 39.9 | 43.1 | 58.8 (1995) |
| Netherlands | 111.9 | 116.9 | 117.4 | 126.2 (1999) |
| Norway | 34.9 | 40.8 | 45.8 | 61.1 (1990) |
| Spain | 45.6 | 52.5 | —† | 71.6 (2005) |

From (*6*).

*Expected peak LCM rate = (LCM rate 1985–1986) + {[(20-year TC slope) × (LCM slope 1975–1985/TC slope 1960–1965)] × (*n* years from 1985 to expected peak year)}, where LCM is lung cancer mortality, and TC is tobacco consumption.

†For countries without lung cancer data for 1985, the slope for 1975–1980 was used, and the rate was projected from 1980 to the expected peak year.

1980s. In Italy and France, lung cancer mortality rates are expected to increase by more than 50% before they peak in 2002 and 2005, respectively. In absolute rates of lung cancer mortality, the peak in Italy is expected to exceed 100/100 000 (rates >100/100 000 have also been reported in Belgium, the Netherlands, and the United Kingdom).

## USE OF TOBACCO-CONSUMPTION MODEL IN DEVELOPING COUNTRIES

The Food and Agriculture Organization of the United Nations predicts that tobacco usage in developing countries will increase almost threefold by 2000 (*17*). Eighty percent of this increase is predicted to occur in Asian countries, where the enormous expansion of tobacco use in the late twentieth century will be associated with a major epidemic of lung cancer in the twenty-first century.

Knowledge of tobacco-consumption rates is all that is needed to apply the simple tobacco-consumption model described in this article to predict the direction of lung cancer mortality rates or even to derive rough estimates of those mortality rates. Although such predictions may not have the accuracy rates achievable with more sophisticated models, they may help health planners in developing countries.

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# Roundtable Discussion: Legal Implications Covering Litigation and Cost of Tobacco Exports[1]

**Gregory N. Connolly (Moderator),[2] Richard A. Daynard,[3] Michael Pertschuk,[4] *and* Judith M. Mackay[5]**

Litigation is a flexible tool for attacking the tobacco industry. Courts are supposed to proceed on the basis of demonstrable facts and settle legal principles and are generally less subject to the industry's political power than legislatures. Judicial proceedings can be used to dramatize the dangers of tobacco use, stymie industry propaganda efforts, reveal nefarious behavior, and force price increases.

American product-liability cases have already produced tremendous media attention. These cases have forced the industry to take the unprofitable propaganda position that anyone who "chooses" to use their products should expect to develop lung cancer, exposed internal industry documents revealing their 35-year-old "stonewalling" and disinformation campaign, and increased tobacco prices. Tobacco litigation has progressed more slowly than expected in the United States, due to judicial rulings that interpreted the 1965 labeling legislation to preempt failure to warn claims, to a tendency among jurors to focus more on the victims' blame than that of the tobacco companies, and to a reluctance among trial lawyers to invest in difficult cases.

Tobacco liability cases may actually be more successful outside the United States, due to the absence of "preemption" clauses in labeling legislation and a less thorough and longstanding knowledge among the general public of the dangers of smoking. Although financing product-liability cases is harder in countries that do not have the American-style contingency-fee system, the availability of government funding (eg, in England) or the work of dedicated volunteers (eg, in Finland and the Philippines) can make tobacco litigation possible. Documents of multinational tobacco companies that are discovered at great cost in one country can be used for little or no cost in another. A plaintiff's verdict anywhere makes the next one more possible to obtain everywhere.

Other types of litigation are also promising. Nonsmokers' cases against employers have been successful in Sweden and Australia; nonsmokers' cases against tobacco companies are also possible and are in the planning stages. A Massachusetts case seeking to force stores not to sell cigarettes to minors can be replicated worldwide. A class action in the Philippines would require multinational companies to impose in each country the strongest warnings they provide anywhere. In Australia, claims by their Tobacco Institute that there is no scientific proof that environmental tobacco smoke causes disease in nonsmokers have been put to the test in an 8-month trial. Finally, in Canada, the defense of action brought by the tobacco industry challenging the constitutionality of Canada's tobacco advertising ban demonstrates that even defending spurious actions initiated by the industry can produce damaging admissions and documents, which can be used by health forces in other cases and in the legislative arena.

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[1] The article by Daynard in these proceedings gives more insight into this roundtable discussion on the legal implications covering litigation and tobacco exports.

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# Tobacco Litigation—Purpose, Performance, and Prospects

Richard A. Daynard[1]

**ABSTRACT—Product liability litigation can dramatize the dangers of tobacco use, stymie industry propaganda efforts, reveal nefarious industry behavior, and force price increases. Recent recognition of nicotine addiction, "discovery" documenting the industry's stonewalling campaign of more than 35 years, and favorable legal developments make future success likely. Litigation can also be used to pressure employers to provide smoke-free working environments, force retailers to obey laws prohibiting sales to minors, require tobacco companies to abandon "colonialist" Third World marketing practices, publicize the falsity of pseudoscientific industry assertions, and prevent television stations from broadcasting tobacco advertising masquerading as sports events. Even defending against harassing legal actions brought by the industry can embarrass the industry and publicly vindicate pro-health groups that oppose it. [J Natl Cancer Inst Monogr 12:53-56, 1992]**

The modern smoking-control movement has attacked the tobacco problem on four fronts. First came the scientific attack on smoking. Smoking was proven to cause lung cancer, heart disease, and other fatal ailments. Smoking-control leaders assumed that, given this proof, the smokers' rational self-interest could be trusted to do the rest. Second, when it became clear that most smokers were not reacting "rationally" and quitting, the attack on smokers began. They were characterized by some people—and often by themselves—as stupid, shortsighted, and hedonistic. Public health efforts focused on scaring smokers or making them feel guilty, and a quit-smoking industry developed to assist them, usually at a price. Third, with the development of the passive smoking evidence, attention shifted to an attack on smoke: let the smokers kill themselves if they insist, but keep nonsmokers out of it.

The last few years have seen the opening of a fourth front. The veterans of the first three fronts, comparing notes, discovered that many of their defeats and frustrations were administered by the same agent: the multinational tobacco industry. (This industry, in its role as antagonist of the smoking-control movement, is referred to as *the tobacco cartel* throughout this article because, when in this role, its members put aside their competitive instincts and work together for their common good.) It was the tobacco cartel that sowed doubts about the validity of the scientific evidence of the lethal and addictive effects of smoking, that promoted their own filter and low-tar cigarettes as the "answer" to the smokers' health concerns, and that single-handedly fought the nonsmokers' rights movement. The time had come to identify the tobacco cartel as the enemy and fight to dislodge it from its positions of power.

The tobacco cartel appears to have an Achilles' heel: its victims have begun to seek justice. Lawsuits are being actively pursued in the United States, Australia, Canada, Great Britain, and Finland seeking compensation for ailing smokers, or their surviving relatives, against cigarette manufacturers. Smoking-control groups in several Asian and Pacific countries, as well as elsewhere in Europe, are seriously considering such actions.

Although each suit involves only one afflicted smoker, the fate of the entire cartel hangs on each one. If any single smoker finally receives justice from a tobacco company, every other victim becomes a potential claimant. If a single plaintiff's attorney is able to make money suing tobacco companies, all plaintiffs' attorneys are thereby encouraged to try. The wound, once opened, cannot be closed. Indeed, developments in individual cases have resulted in 5%–10% increases or decreases in the values of tobacco stocks, whereas the specter of litigation has depressed the companies' share values by 30% or more. Although the cartel can easily defend 100 suits or even pay out a few million dollars in damages, it could not effectively defend 10 000 suits or pay out tens of billions of dollars.

Even more modest scenarios could wreak havoc with the cartel's operations. To begin with, substantial expenses have to be passed on to consumers. In the United States, one round of price increases for both cigarettes and smokeless tobacco has been attributed to the companies' attorneys' fees incurred in their thus far successful defense efforts. Any substantial number of plaintiffs' victories would surely force at least a 10% price increase, and any such increase would, based on past experience, produce a 12% drop in smoking among teenage boys. Larger victories would produce even greater drops. Because perhaps a million youngsters start smoking each year in the United States alone, declines in tobacco use of this magnitude will eventually save tens of thousands of lives annually.

Second, the very process of defending these suits has been costly to the industry's image. The so-called discovery process, the legal procedure by which plaintiffs' attorneys rummage through the industry's files looking for incriminating evidence, has uncovered internal industry documents beginning in the 1930s demonstrating its members' knowledge of the proven health consequences of smoking, and papers from the 1950s and 1960s docu-

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menting the conspiracy among the companies—the cartel—to pretend they cared about their customers' health, genuinely doubted the scientific evidence, and were engaged in bona fide investigations to find the truth. This evidence has received wide publicity and has helped accelerate the decline of the industry's already low reputation and the willingness of legislators to proceed aggressively against it.

The industry's legal defense has also had a public relations aspect that, although successful in swaying juries against tobacco plaintiffs in the short term, has been poisonous to the cartel's long-term interests. The cartel's position, vociferously urged by its lawyers in press briefings and media appearances, is that anyone who smoked bears "personal responsibility" for the resulting lung cancer, because any American who has not lived in a cave since the 1950s (one of their favorite ways of putting it) must have known that scientists were saying that smoking could kill you. The point is both a nasty reminder to their current customers of the foolishness of continuing to use their products and a dramatic concession that only a fool would have believed their continued protestations that the dangers of smoking had not been proven.

Finally, even the modest victories scored against them to date have helped undermine the cartel's aura of invincibility. The June 1988 jury verdict in *Cipollone v. Liggett Group, Inc.* (*1*), although vacated in January 1990 and returned for a new trial, showed that the industry was not beyond the reach of the law. The allegations of jury tampering in *Horton v. American Tobacco Co.* (*2*), which was tried to a hung jury in January 1988, showed an industry that was desperate and on the run. That case was retried in the fall of 1990, with the jury concluding that the tobacco company was at fault for failing to warn of the dangers before being required to do so in 1966. Unfortunately, the jury was not fond of the plaintiff and did not award any damages to his family: both sides have appealed. A case in Finland has had several hearings before the Helsinki City Court and will probably be decided early in 1992, but it has already achieved two advisory rulings from the Helsinki Consumer Complaint Board that the plaintiff should prevail.

Although the industry has usually raised questions about the cause of the plaintiff's cancer, their principal defense has been based on the widespread publicity in the US media of the epidemiological and laboratory studies beginning in 1950, the front-page status of the findings of the 1964 Surgeon General's Report, and the fact that warning labels have appeared on every package of cigarettes sold in the United States since 1966.

This defense has both a technical legal aspect and a so-called common sense aspect. The legal issue, known as preemption, is whether Congress, when it passed the cigarette-labeling legislation in 1965, intended to prevent courts from considering whether the simple act of placing the warnings on their packages completely satisfied the manufacturers' obligation to communicate to their customers and potential customers the full range and extent of the dangers from using their products. Beginning in 1986, five federal appeals courts concluded that the 1965 legislation should be read that way. Some even went so far as to conclude that Congress intended to permit the companies to tell direct and deliberate lies about the safety of their products, as long as they continued to put the mandated warnings on the packages. In July 1990, a high-level court finally disagreed, when the New Jersey Supreme Court concluded that Congress had intended no such thing; in February 1991, a Texas appellate court joined them in this conclusion. The following month, the US Supreme Court agreed to review the issue in the case of *Cipollone v. Liggett Group, Inc.* (*3*). The plaintiffs were supported by friend-of-the-court briefs from a wide range of public health groups, including the American Cancer Society, American Medical Association, American College of Chest Physicians, and the six former surgeons general of the United States. Oral arguments were held on 8 October 1991 and again on 13 January 1992, with a final decision expected in the spring of 1992. However, unless and until the Supreme Court decides the issue favorably for tobacco plaintiffs, it will continue to haunt tobacco litigation in the United States.

Unlike the preemption defense, the common sense objection to tobacco litigation (ie, that every US smoker has been hearing about the public health findings on smoking and health and reading the surgeon general's warnings on the packages for 25 years) cannot disappear at the stroke of a judicial pen. Answering this objection requires, instead, that jurors understand the addictive nature of tobacco use, the fact that most smokers have already become addicted by the time they reach maturity, and the role of the tobacco cartel's massive disinformation campaign in encouraging youngsters to take up smoking and in discouraging smokers from making the necessary efforts to quit. Public awareness of these facts has increased dramatically in the last few years, greatly improving the prospects for favorable jury verdicts.

A case brought forward in most of the countries represented in this conference would not face these objections. In most countries other than the United States, a person did not have to live in a cave to have missed hearing about the 1950s studies or the 1964 Surgeon General's Report. Most countries have not—like the United States—had warning labels for 25 years, and many of the warning labels in other countries are not even as strong as the tepid US labels.

Thus, it is the non-Americans at this conference who may be able to make the best use of tobacco-product liability suits in the immediate future. Whereas most attendees do not have the benefit of the contingent-fee system, which encourages plaintiffs' attorneys to finance the cases in hope of future reward, legal systems exist that are generally much less expensive to use than the US system, and many potential cases exist that would be more difficult for the industry to defend than the US cases. Because in most countries with an open market a substantial proportion of the cigarettes are manufactured by subsidiaries or licensees of the multinational tobacco cartel, the incriminating documents that have been obtained through

the discovery process in the United States and Canada are available for use as evidence in any country in which their products are sold. Perhaps most significantly, these companies can generally be castigated for using weaker warnings, and higher tar and nicotine levels, in other countries than they do for comparable brands in the United States.

The filing of such lawsuits produces tremendous publicity in local media, emphasizing the fact that real people (not just statistics) develop disabling or fatal diseases from smoking and highlighting the duplicitous behavior of the multinational defendants. Each legal development in any case can be the basis for additional such publicity. A victory in any country will not only strengthen immeasurably the smoking-control movement in that country but also demonstrate throughout the world the vulnerability of the particular multinational defendants, as well as of the multinational tobacco cartel.

For example, a promising legal action was taken in late 1990 in Australia, where an asbestos manufacturer was sued by a former employee who contracted lung cancer, a 40-year pack-a-day smoker who had worked in its mine for 7 months in 1961. The asbestos manufacturer expected to be ordered to pay full damages for the lung cancer, and it brought a claim against the cigarette manufacturers for contribution. Although the employee eventually dropped this case, the asbestos manufacturer will presumably take similar action in the future. Should such a claim be successful at trial, it will set a worldwide precedent for cigarette industry liability for its share of this synergistically caused result.

In addition to product liability suits seeking damages for already afflicted smokers and their families, there are four other types of lawsuits that smoking-control forces have brought or supported and that have added strength to the movement and made life more difficult for the tobacco cartel. First are suits brought by nonsmokers either to obtain recognition of their right to a smoke-free workplace or to obtain compensation from their employers for injuries due to secondhand smoke. This litigation has been brought on a wide variety of legal bases (eg, negligence, worker-compensation statutes, laws protecting the rights of the handicapped, and court decisions protecting people who complain about secondhand smoke from retaliation by their employers) and has resulted in substantial money judgments or settlements for afflicted nonsmokers in Australia, Sweden, and the United States. At least equally important, the fear of such litigation has helped prod employers to ban or limit workplace smoking.

This type of litigation will be assisted greatly by a landmark decision in a case brought by the Australian Federation of Consumer Organizations (AFCO) against the Tobacco Institute of Australia. The Tobacco Institute had run an advertisement in 1986 in Australian newspapers—similar to ones that have run in the United States and elsewhere—asserting that "there is little evidence and nothing which proves scientifically that cigarette smoke causes disease in non-smokers." AFCO sought an injunction to prevent the Tobacco Institute from ever running such an advertisement again. The Federal Court of Australia heard testimony over a 9-month period and even took testimony in London from Sir Richard Doll and Drs. Nicholas Wald, Dimitrios Trichopoulos, and Dwight Janerich. On 7 February 1991, the court granted the injunction; in a 210-page opinion, the judge carefully analyzed and rejected the industry's pseudoscientific arguments, holding instead that there was "compelling" evidence even in 1986 that passive smoking caused lung cancer and "overwhelming" evidence that it caused asthma and respiratory diseases in children (*4*).

A second variant on the traditional product liability case is the interesting class-action suit brought in the Philippines by five attorneys and their families, seeking to force the domestic licensees of Philip Morris and R.J. Reynolds to put the same labeling on cigarettes in the Philippines as they do in the United States and to remove their advertising from radio and television as they have in the United States. The defendants actually suggested that by failing to put warning labels on Philippine cigarettes they are not behaving in a racist or colonialist spirit because, they claim, there is evidence to believe that Philippine lungs are hardier than American lungs.

Third are the cases being brought by the Australian smoking-control movement to punish television stations that broadcast cigarette advertisements masquerading as sports events. Recently, the Australian Supreme Court upheld the prosecution of a television station on this basis, demonstrating a refreshingly subtle and accurate analysis of the techniques by which cigarette companies subvert advertising restrictions, as well as an unusual determination that the spirit of the law be enforced.

A fourth type of lawsuit has been pioneered by Group Against Smoking Pollution of Massachusetts. *Kyte v. Store 24, Inc.*, the test case, involved two teenage smokers who sued a chain of convenience stores for illegally supplying them with cigarettes while they were underage, with the result that they are now addicted. In addition to seeking money damages sufficient to cover the cost of monitoring their future medical condition for signs of developing lung cancer or other smoking-induced diseases, they sought an order requiring the stores to obtain positive identification from young people wanting to buy cigarettes, as they do with people wanting to buy alcohol. A preliminary ruling was won early in the litigation establishing that proof of a sale to a minor would automatically constitute a violation of the state consumer protection act, which would also permit the plaintiffs to recover attorney's fees from the convenience store chain if the case went to trial. In the face of that ruling, the chain settled the case in June 1991, agreeing to demand proof of age from young would-be cigarette purchasers.

All of these suits are important not only for the specific judicial relief they seek but also for the tremendous publicity they generate and the momentum they add to other smoking-control measures.

A different type of suit was brought by the tobacco cartel in an effort to bring the smoking-control movement to heel. These suits are varied, including a trade infringement suit brought by Philip Morris' beer subsidiary

against Alan Blum and Doctors Ought to Care for selling T-shirts ridiculing a promotional event, an effort by the Swedish tobacco industry to get the legal ombudsman to suppress the clever and very effective "Smart Promotion" booklets distributed by government and private agencies, an effort by the Dutch tobacco industry to force health groups to apologize for suggesting that secondhand smoke is dangerous, and the effort of the Canadian industry to have Canada's tobacco advertising ban declared violative of the free-speech provisions of the Canadian Charter.

Many of these bullying tactics appear to have backfired. Philip Morris quickly withdrew its complaint over the T-shirts after the *Wall Street Journal* ridiculed Philip Morris' lack of humor and *Time Magazine* criticized its hypocrisy in purporting to love the First Amendment's protection of speech but only when it comes to tobacco advertising. The Swedish legal ombudsman refused to interfere with Smart Promotion, except to require that it not use a parody of a Camel ad for its front cover. The Dutch court decided (amid substantial publicity) that the health groups behaved properly in warning of the dangers of environmental tobacco smoke, and the tobacco companies later agreed to dismiss their complaint and to pay the health groups' litigation costs.

The Canadian action has, however, resulted in a trial court ruling favorable to the industry. On 26 July 1991, Judge Jean-Jude Chabot of the Quebec Superior Court ruled that the Canadian law requiring strong labels and banning tobacco advertising unconstitutionally encroached on provincial powers and violated the free-speech rights of the tobacco industry (*5*). Judge Chabot's opinion reflected his strong aversion to the type of "social engineering" represented by Canada's Tobacco Products Control Act; he did not demonstrate, however, that his aversion was shared by the Canadian Supreme Court. The Attorney General of Canada appealed the case to the Quebec Supreme Court on 14 August; a further appeal to the Canadian Supreme Court is available and would probably be successful.

There are, however, "silver linings" in developments in the case to date. The evidence presented at trial has already resulted in the release of industry documents revealing how their marketing devices have been targeted at adolescents. Judge Chabot himself commented that

> The uncontested evidence provided by the Attorney-General of Canada indicates clearly and undeniably that tobacco addiction has been seen, both in Canada and in the international community, as a scourge for a great number of years. The masses of information gathered in Canada and throughout the world, particularly during the last 25 years, makes it abundantly clear that tobacco use constitutes a substantial and urgent problem in Canada, in a free and democratic society, and more generally in the global community. It is the opinion of this court that the fight against tobacco constitutes a sufficiently important objective in a free and democratic society such as ours to justify the restriction of freedoms guaranteed by the Canadian Charter of Rights and Freedoms.

The tobacco industry has shown an extraordinary ability to deflect, neutralize, or at least blunt the most pointed and promising public-health campaigns aimed against it and its products. As Beth Whelan has said, whenever we throw lemons at them, they turn around and make lemonade.

Efforts must continue, however, because the stakes are too high. Public-health campaigners must therefore behave like the biblical David, circling the tobacco Goliath, looking both for a rock that can be lifted and a weak point that can be hit. Tobacco litigation of the kinds described in this article is within the financial reach of many pro-health organizations; if even a few of these cases hit their mark, smoking-control efforts may destroy the industry's credibility, cripple its ability to lie about the dangers of its products, and seriously impede its efforts to market cigarettes to children.

## REFERENCES

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# Advocating on Behalf of the Facts

**Michael Pertschuk**[1]

It is curious that these proceedings of a conference on cancer research begin with a section that is devoted to "facts." These proceedings are divided into facts, maybes, and rumors, but the issues that are classified as facts are presumably those for which research is no longer necessary.

There is no doubt that the role of tobacco as a causative agent of disease is fact. I am reminded of my first encounter with Joe Cullen at a meeting of the Interagency Council on Tobacco Research in the early 1980s. Because he was from the National Cancer Institute, I expected a quiet, mild, but academic approach to cancer research; but his first words were, "Anybody who funds any more basic research on the relationship between tobacco and disease ought to be put in jail."

So why are we here? Because the facts about tobacco and disease have thrust us into a worldwide campaign in which the goal, the elimination of the use of tobacco, is certain, but the methods of achieving that goal have led us into a thicket of maybes. There is good reason to believe that comprehensive tobacco control plans and programs will help achieve the goal of a smoke-free society and that these plans must include such elements as building national, state, local, and international governmental and nongovernmental tobacco-control coalitions.

Advertising and promotion must be banned. We need to limit young people's access to tobacco. We need high and ever-higher tobacco taxes. We must strictly limit smoking in public places and workplaces. Public education in schools and in the media must be both aggressive and subtle. We must track and counteract the prosmoking public relations propaganda and political action strategies of the tobacco companies, and we need smoking-cessation programs. However, although we are certain that these strategies taken together will work, there remain many maybes to answer that can help us refine these strategies.

The maybes include the following questions. What forms do the most effective tobacco-control coalitions take? How do we prioritize among policy goals? Which are the most effective, cost-effective, and synergistic with other policy goals? What are the most effective advocacy strategies toward achieving policy goals? What are the most effective answers to the tobacco industry's arguments against action? How can policy research help us formulate better answers? For example, how can economists help us better respond to the industry's claim that tobacco is really healthy for the economy?

If we visualize the tobacco companies as the viral agents of smoking-caused disease, how can we place that viral agent under the research microscope to better understand its actions and devise antidotes?

One of the tragic environmental ironies of our time is that, as the benign rain forests in the less developed world shrink, the virulent tobacco leaf expands into the far reaches of that unprotected world. Therefore, we also must find ways of strengthening communications systems and strategies to better transmit the knowledge we have acquired in developed countries for the strategic benefit of threatened, lesser developed countries.

Joe Cullen understood that there still was much to learn about the control of tobacco-caused disease, although he believed that it would be criminal to hesitate before applying the remedies we have reason to believe work.

The extraordinary array of tobacco-control experts in these proceedings is as well equipped as any in the world to present collectively what we know to be the facts about tobacco and what we need to know—in short, what is now the remaining tobacco-control research agenda.

Tobacco-control research should take a more central place on the future agenda of cancer research; DeVita's address invited the development of better-structured research proposals in these fields. Although much of this research is not elegant, it will lead directly to the sparing of vast numbers of cancer deaths. And that, it seems to me, is why we are here.

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# International Differences in Diet and Cancer Incidence[1]

Maureen M. Henderson[2]

**ABSTRACT—International variations in the annual incidence rates of reproductive organ and gastrointestinal cancers suggest that they have environmental causes and can be controlled by public health approaches. Secular trends in the national incidence rates of these two groups of tumors and the experiences of migrants moving from countries with low rates to countries with higher rates of these cancers increase the likelihood that public health dietary interventions will lower cancer incidence rates. The results of recent correlation analyses of international variations in the consumption of dietary fat and incidence of large-bowel and hormone-dependent reproductive organ cancers suggest that both the total amount of fat and the specific fatty acids consumed are associated with the incidence of these cancers in national populations and that the associations strengthen with age and are strengthened rather than weakened by the inclusion of potentially confounding and modifying dietary and nondietary factors in the analysis. The consistency of estimates developed with coefficients derived from these analyses and the degree to which they agree with independent observations suggest that they can provide useful parameters for the design of trials to test the hypothesis that they measure causal associations. [J Natl Cancer Inst Monogr 12:59–63, 1992]**

International variations in the annual incidence rates of breast, colon, and prostate cancers point to the existence of one or more environmental causes that could be controlled, to some extent, by public health interventions (*1*, *2*). Results of observational studies among migrants from countries with lower incidence rates to countries with higher incidence rates of these cancers have reinforced this suggestion because of the rapidity with which the newcomers' cancer rates have increased in the 20 years after migration (eg, migrants to Australia and Israel) (*3*, *4*; Modan B: unpublished observations). It has also been reinforced by the rate at which incidence of breast cancer has risen in a relatively short time within countries such as Japan as the amount of fat in the diet increased (*5*, *6*). Most of the original hypotheses about the influence of diet on human cancers were developed from the results of experimental feeding studies in rodents (*7–9*). A series of controlled statistical analyses of the range of international variations in the rates of these three cancers in association with per-capita disappearance of grams of fat (average fat consumption) were carried out in an effort to develop more specific causal hypotheses from human data and to prepare estimates to be used in the design of dietary intervention trials to test the hypothesized causal relationships (*2*, *10–12*).

## METHODS

Criteria established by Armstrong and Doll (*13*) were used to select countries with reliable and (nationally) representative registries from all those with reported cancer registrations. Twenty-one countries met the criteria. Age-adjusted cancer incidence rates were calculated for each of these countries for the period 1973–1977 with information from *Cancer Incidence in Five Continents* (*14*). In line with Armstrong and Doll, the rates were truncated to ages 35–64 years to limit bias from variations in rates of misclassification of disease incidence in the elderly and of populations at risk. All analyses were controlled for estimated calorie intake with methods proposed by Willett (*15*). United Nations Food and Agriculture Organization records for 1975–1977 were used to calculate the average national consumption of the individual fatty acids provided by the most common food groups (*16*). In each country, 68 fat-containing food items providing 90% or more of the fatty acids consumed were each broken down into the amount of saturated, polyunsaturated, monounsaturated, n-6, and n-3 (from fish) they provided. This analysis is described in detail by Hursting et al. (*10*). All hypotheses to be tested were specified before any analysis was executed.

The first regression analyses with estimates of individual fatty acids eaten addressed the hypotheses, based on the results of animal experiments, that grams of both saturated and polyunsaturated fats would be strongly associated with the incidence of breast, prostate, and colon but not lung and cervical cancers; monounsaturated fat would have no association with any cancer; and n-3 fatty acids from fish would tend to be negatively related to cancers associated with the amount of fat consumed (*10*). Age-specific analyses were carried out for cancer of each site that was positively associated with the average total fat consumption. All of these analyses were controlled for estimated total calorie intake. Prentice et al. (*2*, *11*, *12*) then explored these hypotheses more intensively.

A series of dietary and nondietary variables available in the published literature were entered into the regression

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analyses. These included protein, carbohydrate, and alcohol calories; retinol; β-carotene; gross national product; height; weight; age at menarche; and tobacco consumption (*11*). These controlled analyses were then repeated for the age-group 55–69 years. Further controlled regression analyses were carried out relating current and prior national disappearance rates of fat-containing foods and international site-specific incidence rates in the early 1960s and late 1970s and international mortality rates for 14 countries in 1962, 1970, and 1978 (*12*). They were also carried out for incidence rates between 1961 and 1963 and 1975 and 1977 in 10 (of the original 21) countries that had available historical data (*2*).

As a final test of the stability of the regression coefficients from analyses of the international variations, they were used to predict cancer incidence rates that investigators ought to find in epidemiological studies of migrants, according to the level of fat consumption in their birth and host countries and the relative-risk ratios investigators would be expected to report for individuals included in their case-control and cohort studies on the basis of the subjects' recorded fat intake (*2*). As an illustration, for Japanese migrants to the United States, the age-adjusted incidence rate of a cancer associated with level of fat consumption in the United States (estimated with the regression coefficients) was divided by the age-adjusted rate of the same cancer in Japan. This ratio was compared with the ratio of observed rates for Japanese migrants residing in the United States divided by the rate in Japan (*17*).

Relative-risk ratios were predicted, with the regression coefficients, for ranges of fat consumption measured in site-specific series of case-control and cohort studies. The same approach was used to calculate relative-risk ratios for different levels of fat consumption by women included in an aggregation of case-control studies of postmenopausal breast cancer. The latter predicted relative risks were compared with estimates reported in a recent independent reanalysis of the data from eight of these studies (*18*).

## RESULTS

Four pieces of information were derived from the results of this increasingly well-controlled series of regression analyses linking national cancer incidence rates and average levels of fat consumption. They were the specific cancer sites strongly associated with fat consumption, the ages at which the statistical associations were strongest, the specific fatty acids that accounted for the associations, and estimates of the quantitative relationship between site-specific cancer incidence and changes in average fat consumption. The results of the first regression analysis identified a hypothesized association between average total fat consumption and the incidence of breast and colon cancer in women and colon and prostate cancer in men and the absence of a strong association with lung and cervical cancer. What initially appeared to be a weak association between lung cancer and fat consumption disappeared when average tobacco consumption was included in the analysis (*10*; table 1).

Virtually all international variations in the average number of total calories eaten are modulated by variations in the consumption of fat. This fact is underscored by the limited range of differences in the average number of nonfat calories. The ratio of highest to lowest average national consumption of nonfat calories is 1:01 compared with 2:2 for total fat grams and 3:6 for saturated fat grams (*10*).

The strong statistical associations of the incidence of breast, colon, and prostate cancer with the percentage of daily calories eaten from fat of all kinds were virtually unchanged by inclusion of nonfat calories into the regression analysis. Nonfat calories themselves had no independent association with variations in cancer ineidence at any of these sites (*11*; table 2). The strength of the associations between these cancers and fat consumption increased steadily with age. Given that the ineidence of these eancers also increases with age, postmenopausal women and older men (55–69 years) were subsequently chosen for purposes of illustration of the potential impact of these findings. The results of the analyses illustrated below for women

**Table 1.**—Partial correlation coefficients between age-adjusted cancer incidence rates and components of dietary fat in 21 countries*†

| Fat component‡ | Cancer incidence | | |
|---|---|---|---|
| | Breast (F) | Colon (F) | Prostate |
| Total fat | .72§ (0.95) | .62§ (0.024) | .69§ (0.23) |
| Saturated fat | .58§ (1.80) | .47 (0.044) | .55§ (0.43) |
| Monounsaturated fat | −.01 (−0.03) | .004 (0.004) | .02 (0.01) |
| Polyunsaturated fat | .51§ (2.70) | −.01 (−0.01) | .46 (0.64) |
| n-6 | .50 (2.50) | −.03 (−0.05) | .46 (0.60) |
| n-3 | −.28 (−23.4) | −.15 (−4.3) | .04 (0.9) |

* Adapted from (*10*). Numbers in parentheses are slope of least-squares relationship based on cases · $100\,000^{-1} \cdot g^{-1}$.

† With reliable and representative cancer registration: Australia, Canada, Denmark, FRG, Finland, France, Hong Kong, Hungary, Israel, Italy, Japan, New Zealand, Norway, Poland, Romania, Spain, Sweden, Switzerland, UK, US, Yugoslavia.

‡ Adjusted for total calories and other fatty acids.

§ $P < .05$; $P$ value of test of partial correlation coefficients = 0.

**Table 2.**—Effects of nonfat calories on regression coefficients: women aged 55–69 years*

| Cancer site | Fat calories not controlled for nonfat calories | | Fat calories controlled for nonfat calories | | Nonfat calories | |
|---|---|---|---|---|---|---|
| | b | *P* | b | *P* | b | *P* |
| Breast | .185 | .0001 | .187 | .0007 | .004 | .94 |
| Colon | .071 | .0004 | .065 | .004 | −.009 | .64 |
| Rectum | .021 | .004 | .021 | .02 | −.0003 | .96 |
| Ovary | .039 | .0002 | .041 | .0009 | .004 | .69 |
| Endometrium | .059 | .0001 | .069 | .0001 | .018 | .12 |

*Adapted from (*2*).

aged 55–69 years were virtually the same for analyses of incidence rates in men in this age-group and men and women in other age-groups.

In regard to specific fatty acids in food, monounsaturated fat was not associated with any cancer studied. Both saturated and polyunsaturated fats were associated with breast and prostate cancers. Only saturated fat had a strong association with colon cancer in both men and women. Although the small quantities eaten made it impossible to study n-3 fatty acids from fish with confidence, correlations were almost always in a negative direction. There was a positive relationship of polyunsaturated (particularly n-6) fatty acids with the hormone-dependent but not the large bowel cancers. The latter finding proved to be consistent in subsequent analyses in all age-groups despite potentially confounding variables.

The results of these analyses and of two feasibility studies of a low-fat intervention (*19*, *20*) were used to estimate the potential reduction in US rates of site-specific cancer incidence from a sustained and populationwide 50% cut in average fat consumption (*2*; table 3). The feasibility studies of a low-fat intervention to prevent breast cancer provided results suggesting that motivated postmenopausal women can and will cut their fat consumption in half and maintain that eating pattern for at least 3 years (table 4).

More extensive analyses included in the series showed that rectal, ovarian, and endometrial, but no other cancers, were also statistically associated with average fat consumption with some degree of confidence. These associations were also strengthened rather than weakened when a series of dietary and nondietary variables were entered with them into the analyses (*2*, *12*). The analyses provided consistent estimates of the amount of change in age- and site-specific cancer incidence rates to be expected from a given reduction or increase in average overall consumption of fat or average consumption of a given fatty acid, within the context of migrant studies (table 5).

The predicted rates of disease in Japanese migrants were almost identical to those reported in the observational study. The risk ratios predicted for aggregated case-control studies among postmenopausal women were also similar to those calculated by an independent meta-reanalysis of eight case-control studies (*2*; table 6).

**Table 3.**—Estimated changes in cancers associated with dietary fat after a 50% reduction in fat consumption among US population aged 55–69 years*

| Cancer site | Age-adjusted US incidence rate/100 000 | | |
|---|---|---|---|
| | 1978–1982 | Estimated for fat reduction | Change, % |
| Women | | | |
| Breast | 257.4 | 100.4 | 61 |
| Colon | 89.9 | 29.7 | 67 |
| Rectum | 40.9 | 29.0 | 29 |
| Ovary | 45.6 | 17.8 | 61 |
| Endometrium | 91.4 | 23.8 | 74 |
| All above | 525.2 | 200.6 | 62 |
| Total cancer | 936.4 | | 33 |
| Men | | | |
| Prostate | 167.6 | 28.5 | 83 |
| Colon | 115.8 | 42.8 | 63 |
| Rectum | 64.6 | 41.3 | 36 |
| All above | 348.0 | 112.6 | 68 |
| Total cancer | 1169.0 | | 17 |

*Adapted from (*2*).

**Table 4.**—Mean daily intake of fat in postmenopausal women assigned to intervention group of low-fat feasibility trial (food-frequency questionnaire)*

| | Intervention month | | | |
|---|---|---|---|---|
| | 0† ($n=184$) | 12 ($n=167$) | 24 ($n=156$) | ~36 ($n=146$) |
| Fat, g | | | | |
| Total | 85.1 | 37.1 | 38.3 | 35.5 |
| Saturated | 30.4 | 13.0 | 13.2 | 12.2 |
| Monounsaturated | 31.9 | 13.2 | 13.5 | 12.7 |
| Polyunsaturated | 16.6 | 5.5 | 6.1 | 5.6 |
| Cholesterol, mg | 355.3 | 165.7 | 162.3 | 149.0 |

*Data from (*20*).
†Different food-frequency questionnaire.

## DISCUSSION

Several approaches are being taken or have been proposed to collect data to strengthen or refute existing evidence in support of causal diet and cancer relationships. They include the collection of diet, nutrition, and health information from representative samples of residents in geographic areas with different cancer rates; international case-control studies in unique populations; detailed diet histories in first- and second-generation migrants who represent groups with reported secular changes in incidence; and controlled correlation analyses of food-consumption and cancer-incidence data. The series of correlation analyses described herein are the consequences of several decades of natural experiments in human nutrition.

The estimates used for purposes of illustration in the figures presented in table 3 were similar whether they were calculated from international cross-sectional data during the 1960s or the 1970s (*2*). They were also similar when they were calculated from mortality rates in the same decades. Even more surprising, they were in the same range when they were calculated from data describing changes in site-specific cancer incidence rates and average consumption of fat within individual countries over periods of 10–20 years (*2*).

**Table 5.**—Comparison of age-adjusted cancer incidence rates for Japanese living in United States versus living in Japan with those projected from international regression analyses*

| Cancer site | Observed 1985† | Projected from regression analyses‡ |
|---|---|---|
| Women | | |
| Breast | 3.5 | 2.9 |
| Colon | 3.2 | 3.5 |
| Rectum | 1.5 | 1.5 |
| Ovary | 2.9 | 2.9 |
| Endometrium | 11.3 | 4.6 |
| Men | | |
| Colon | 3.5 | 3.0 |
| Rectum | 2.3 | 1.6 |
| Prostate | 5.7 | 7.2 |

*Adapted from (*2*).
†Data from (*17*).
‡Assuming change from average per-capita fat calories in Japan to average in United States in 1975–1977.

**Table 6.**—Relative risks of breast cancer for fat-consumption quintiles*

| | Fat-consumption quintiles | | | | |
|---|---|---|---|---|---|
| Risk ratios | 1 | 2 | 3 | 4 | 5 |
| Predicted for age 55–69 y from international regression analysis (*2*) | 1 | 1.07 | 1.15 | 1.26 | 1.53 |
| Estimated from eight case-control studies in postmenopausal women (*18*) | 1 | 1.20 | 1.24 | 1.24 | 1.56 |

*Adapted from (*2*).

The stability of these estimates of the quantitative relationship between cancer incidence rates and the average amount of fat eaten, together with the results of animal carcinogenesis experiments, argues a need for experimental studies. The stability of the results of these analyses gives confidence that credible research designs can be developed for these purposes.

An intermediate phase between the analyses of international variations and nutritional experiments might include comprehensive plans to document the extent to which national food-consumption data reflect the fat consumption of men and women of different ages in different countries, as well as plans for research that would exploit the existence of international differences in disease incidence. For example, a search for useful short-term end points that would expedite and reduce the cost of badly needed prevention trials might be more productive in countries with low rates of disease than in countries with high rates and might be most productive in countries with rapidly changing incidence rates. Intervention trials that randomize individual subjects and cohort studies are in process within countries, but there is still no organized plan for similar collaborative international efforts.

Our interpretation of the consistent findings of associations between the incidence of specific cancers and saturated, polyunsaturated, and total fat is that, whereas the total amount of fat eaten determines cancer incidence rates, these rates are moderated further in sensitive cancer sites by additional independent influences of saturated and n-6 polyunsaturated fatty acids. These independent statistical influences argue against the sole impact of dietary fat on cancer incidence being mediated through the energy it provides.

Gram for gram, each fatty acid provides the same number of kilocalories. If fat influenced tumor growth solely through the provision of calories, monounsaturated, saturated, and n-6 and n-3 polyunsaturated fatty acids should all have exactly the same site-by-site associations. The lack of any association of cancer incidence with monounsaturated fat consumption was predicted by the results of

animal studies but is more remarkable when considering that much monounsaturated fat in the human diet comes from the same foods that supply saturated fat.

If studies of the validity of national food-consumption data had been satisfactorily completed and some short-term outcome measurements had been found, more innovative, collaborative international studies could even now be under consideration. The opening up of underdeveloped areas of the world, spreading industrialization, the breakdown of international boundaries, and the establishment of new independent economies all have the potential to influence local, regional, or national food supplies and habits. There must be many imaginative ways to integrate responsible observational studies into these settings.

In the long term, the strongest evidence for a dietary cause of one or more cancers would come from successful intervention in numerous countries with different overall food patterns and sources and different exposures to potentially confounding factors such as the use of exogenous hormones. The most opportune intervention may be preventing a potential increase in fat consumption rather than cutting down an established high consumption.

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# Life-Style and Cancer: From Epidemiological Evidence to Public Behavior Change to Mortality Reduction of Target Cancers[1]

Takeshi Hirayama[2]

**ABSTRACT—Cigarette smoking, alcohol consumption, and diet are of essential importance in modulating risks of cancer of selected sites, as demonstrated by various epidemiological methods. Examples include demographic studies on changing cancer risk, correlation studies on dietary fat and cancers of breast and colon, and case-control studies on highly salted food and gastric cancer. Evidence was also obtained by cohort studies including a census-population-based large-scale prospective study in Japan. Results included elevated risk from cigarette smoking for cancers of most sites; from alcohol consumption for cancers of the upper and lower digestive tract, liver, and prostate; and from daily meat consumption for cancers of the pancreas, colon, lung, and breast. Daily consumption of green-yellow vegetables reduced risk for cancer of the stomach, colon, lung, cervix, and prostate. Reports of these results and intensive public education and public guidance by governmental and nongovernmental organizations such as cancer societies, consumer groups, and mass media resulted in a notable change in public behavior in most cases in Japan. [J Natl Cancer Inst Monogr 12:65–74, 1992]**

There is ample evidence that cancer risk in humans is strongly influenced by individual life-style. Among many life-style variables, cigarette smoking, alcohol consumption, and diet are the main factors determining the risk of developing cancer. This conclusion was obtained by various epidemiological methods (fig. 1). These epidemiological studies commonly focus on identification of risk factors and establishment of strategies for primary prevention, modification of public behavior, and reduction of cancer mortality. I present evidence from Japanese studies.

## MATERIALS AND METHODS

Cancer mortality statistics for Japan are published each year as part of the Vital Statistics by the Ministry of Health and Welfare. Statistics for 1955–1988 were used in this study.

The census-based large-scale cohort consisted of 265 118 adults (122 261 men, 142 857 women) aged ≥40 years (94.8% of 1965 census population) (*1*). The subjects were interviewed by public health nurses about life-style variables such as smoking, drinking, diet, reproductive history, and occupation from 1 October to 31 December 1965 in 29 health-center districts in six prefectures (Miyagi, Aichi, Osaka, Hyogo, Okayama, and Kagoshima) in Japan (*1*; fig. 2). These subjects were followed for 17 years (1966–1982). The rate of follow-up was nearly 100% when subjects remained in the same health-center districts. Those who migrated from the original health-center district were tabulated separately. A census was performed annually to ascertain that subjects still resided in the health-center districts. A record-linkage system was established among original risk-factor records, residence records, and death certificates collected continuously throughout the study. Tabulation and analysis were done by computers.

A case-control study on diet and gastric cancer was performed in 1960–1961 in Kanagawa prefecture. In this study, 454 patients (300 men, 154 women) with gastric cancer and 454 sex-, age-, and occupation-matched control subjects were compared as to life-style, including dietary habits.

A national nutrition survey was conducted annually by the Ministry of Health and Welfare of Japan from 1955 to 1988 for 6000 households (20 000 family members) selected randomly. A trained dietitian investigated details of meals eaten for 3 days and measured physical characteristics such as height, weight, skin thickness, and blood pressure.

## RESULTS

### Salted Food and Gastric Cancer

Frequent consumption of highly salted food, widely used in Japan, was identified as the major reason for the extremely high incidence of gastric cancer in Japan (*2*; fig. 3). The correlation study showed that the higher the concentration of salt in soybean paste, mainly used for pickling, the higher the gastric cancer mortality. The case-control study of gastric cancer showed the relative risk of gastric cancer increased in both men and women the more frequently salty foods were consumed. The change in public behavior and reduction of gastric cancer mortality were

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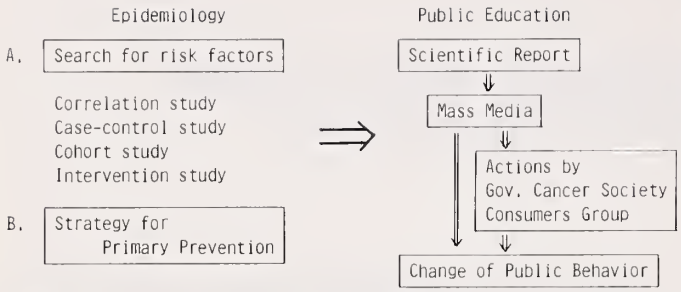



**Figure 1.**—Missions of epidemiological research.

confirmed by a series of laboratory studies (*3*). When the close association of salty food and gastric cancer was widely reported, a vigorous campaign to reduce salt consumption was spread countrywide by a team of oncologists, cardiologists, and consumer groups. Aided by the introduction of electric refrigerators, the public in Japan responded by reducing per-capita daily salt consumption by 16% in 17 years, from 14.5 g in 1971 to 12.2 g in 1988, resulting in a drastic reduction of gastric cancer mortality, ie, over 50% reduction in 30 years. These sequential events can be considered a model for the plan shown in figure 1: ie, epidemiological research for identification of risk factors and for establishment of a strategy for primary prevention, actions to modify public behavior as indicated by this epidemiological research, and eventual reduction in mortality of the target cancer.

## Cigarette Smoking and Cancer

As revealed by the cohort study, cigarette smoking is clearly the most potent risk factor for cancer of all sites and for conditions such as aneurysm, subarachnoid hemorrhage, ischemic heart disease, hypertensive heart disease, bronchial asthma, emphysema, and peptic ulcer (fig. 4). For lung cancer, earlier age at start of smoking and amount of smoking were observed to independently raise the risk (*4*; fig. 5). After smoking cessation, the lung cancer risk was found to gradually approach the level of nonsmokers. A passive smoking effect was also apparent (*4, 5*). Nonsmoking wives of smoking husbands showed elevated risk of lung cancer in 20 of 25 studies reported between January 1981 (*6*) and the end of 1990 (fig. 5). In addition, risks of lung cancer, breast cancer, and ischemic heart disease were significantly associated with smoking husbands even when meat consumption, a probable confounder, was adjusted (fig. 5).

The public responded to the evidence of smoking hazards with a reduction in smoking rate of 28% during the past 25 years. About 10 million adults stopped smoking during this period in Japan, which is an example of successful implementation of results of epidemiological research in modifying public behavior.

## Alcohol Consumption and Cancer

Age-standardized mortality ratio or relative risk of alcohol consumption was calculated for cancer of each site. Besides cancers of the upper digestive tract (mouth, pharynx, esophagus), cancer of the sigmoid colon was uniquely associated with alcohol consumption (*7*; fig. 6). This association was even stronger than that for high-fat, low-fiber diets, with the relative risks of consumers over rare consumers or nonconsumers being 3.95 for alcohol, 2.59 for milk, 1.79 for meat, 1.42 for cigarettes, 0.76 for fish, 0.44 for rice/wheat, 0.36 for green-yellow vegetables (GYV), and 0.30 for soybean paste soup.

Alcohol-related cancers were classified according to interaction with cigarette smoking (fig. 7). Interaction affected cancers of the mouth and pharynx, esophagus, liver, and urinary bladder. Interaction did not affect cancers of the sigmoid colon, rectum, or prostate.

## Fat and Cancer

Meat consumption was positively associated with cancers of the breast, ovary, and pancreas. Interaction with cigarette smoking appeared to affect these cancers (fig. 8).

Evidence for a close association between breast cancer and high fat consumption (*8*) was obtained from correlation studies by countries (*9*), by ethnic groups in Hawaii (*10*), and by each district in Japan; from cross-sectional studies by per-capita fat consumption in metropolitan areas, cities, and counties in Japan; and from our cohort study (fig. 9). Daily meat consumption was noted as the leading risk factor of breast cancer among many life-style variables studied, relative risk being 1.83. The association was particularly apparent in postmenopausal women, showing a typical Western-type age curve in daily meat consumers and a typical Japanese-type age curve in nondaily meat consumers.

In Japan, up to 1973, both per-capita animal-fat consumption and breast cancer mortality sharply increased, probably as the result of Westernization of Japanese lifestyles. Therefore, the future trend was predicted by fitting and extrapolating a log-quadratic curve to the trend from 1955 to 1973. It was estimated that both animal-fat consumption and breast cancer mortality might approach the US level by 1988. Surprisingly, however, the increase in animal-fat consumption virtually stopped after 1974 (fig. 10; 1973 was the year of the first oil crisis). Again, the increasing trend of both breast and colorectal cancer slowed significantly since that year. No such tendency was

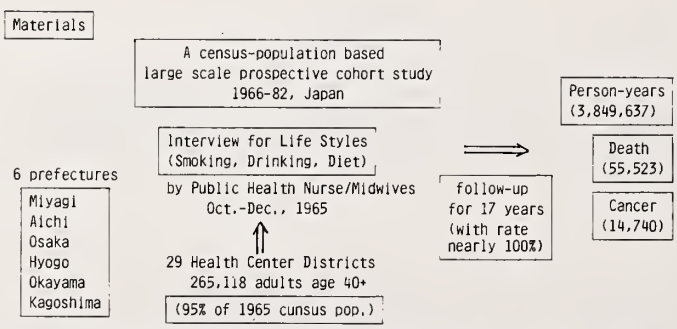
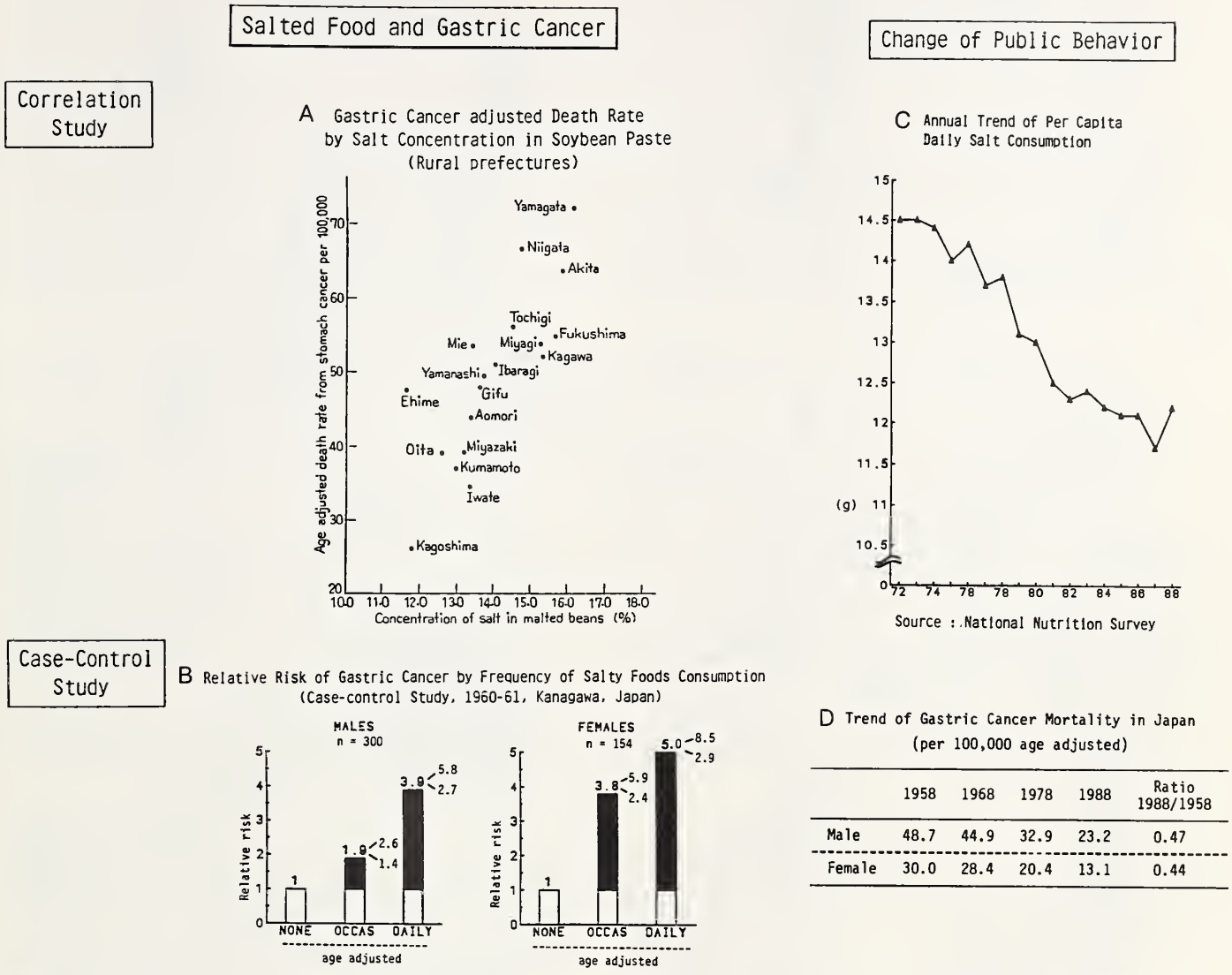



**Figure 2.**—Census-population-based large-scale prospective cohort study, 1966–1982, Japan.




| | 1958 | 1968 | 1978 | 1988 | Ratio 1988/1958 |
|---|---|---|---|---|---|
| Male | 48.7 | 44.9 | 32.9 | 23.2 | 0.47 |
| Female | 30.0 | 28.4 | 20.4 | 13.1 | 0.44 |

**Figure 3.**—Results of correlation (A) and case-control (B) studies on salted food and gastric cancer and their effects on public behavior change (C) and eventual mortality reduction of gastric cancer (D).

observed for cancer of other sites (fig. 10). The parallel reduction of the ratio of observed to expected or estimated value was impressive, suggesting a promising effect of animal-fat consumption control on prevention of breast cancer (especially postmenopausal) and colorectal cancer. Although these values are relative to estimated trends, the parallel reductions of animal-fat consumption and breast and colorectal cancers show the importance of planning strategies for control of these cancers.

### Green-Yellow Vegetables and Cancer

The lower the frequency of GYV consumption, the higher the risk of cancer of all sites and, specifically, stomach and colon cancers. (fig. 11). For lung and cervical cancers, the effect was most striking in heavy smokers.

Because GYV is defined by the high concentration of β-carotene, and β-carotene is considered one of the potent scavengers of oxygen radicals, the positive association between GYV and cancer is interpreted as mainly resulting from the beneficial action of β-carotene–rich GYV. In addition, the vitamin C, minerals such as calcium and iron, and dietary fiber of GYV must also play a role in reducing cancer risk. For stomach cancer, the increase in GYV consumption, even after reaching adulthood, was shown to reduce the subsequent risk (fig. 11).

Further merits of consuming GYV daily include effects on passive smoking, ie, decreasing the extent of risk of lung cancer in nonsmoking wives of smoking husbands (*5*), and acceleration of effects of smoking cessation, ie, faster reduction of lung cancer risk to nonsmoker's level when GYV was consumed daily (*1*). Daily consumption of meat and GYV decreased the risk of cancers at many sites. In contrast, in nondaily consumers of GYV, daily meat

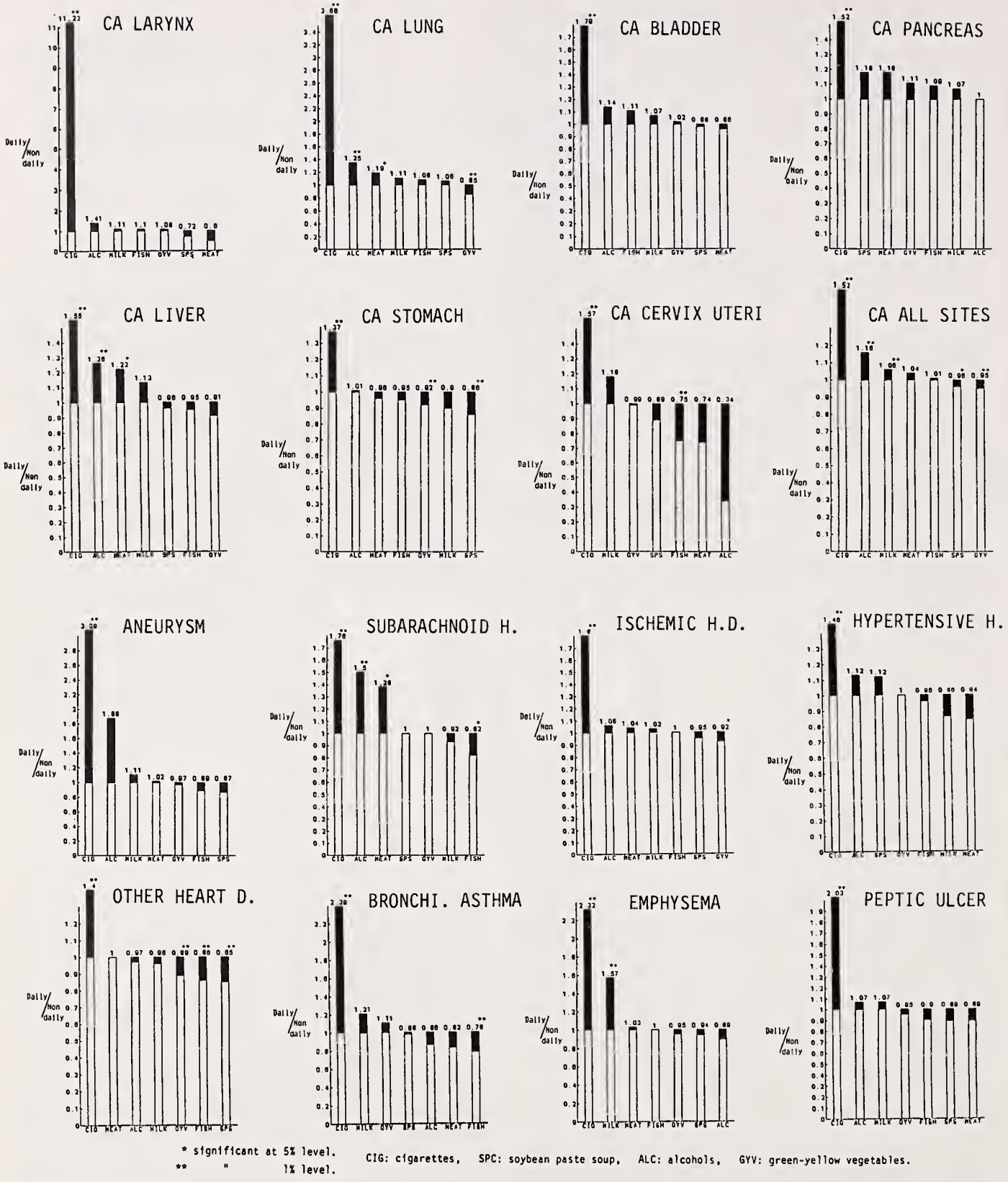



**Figure 4.**—Sex- and age-standardized mortality-rate ratio by selected life-style variables. CA, cancer. Cohort study, 1966–1982, Japan.

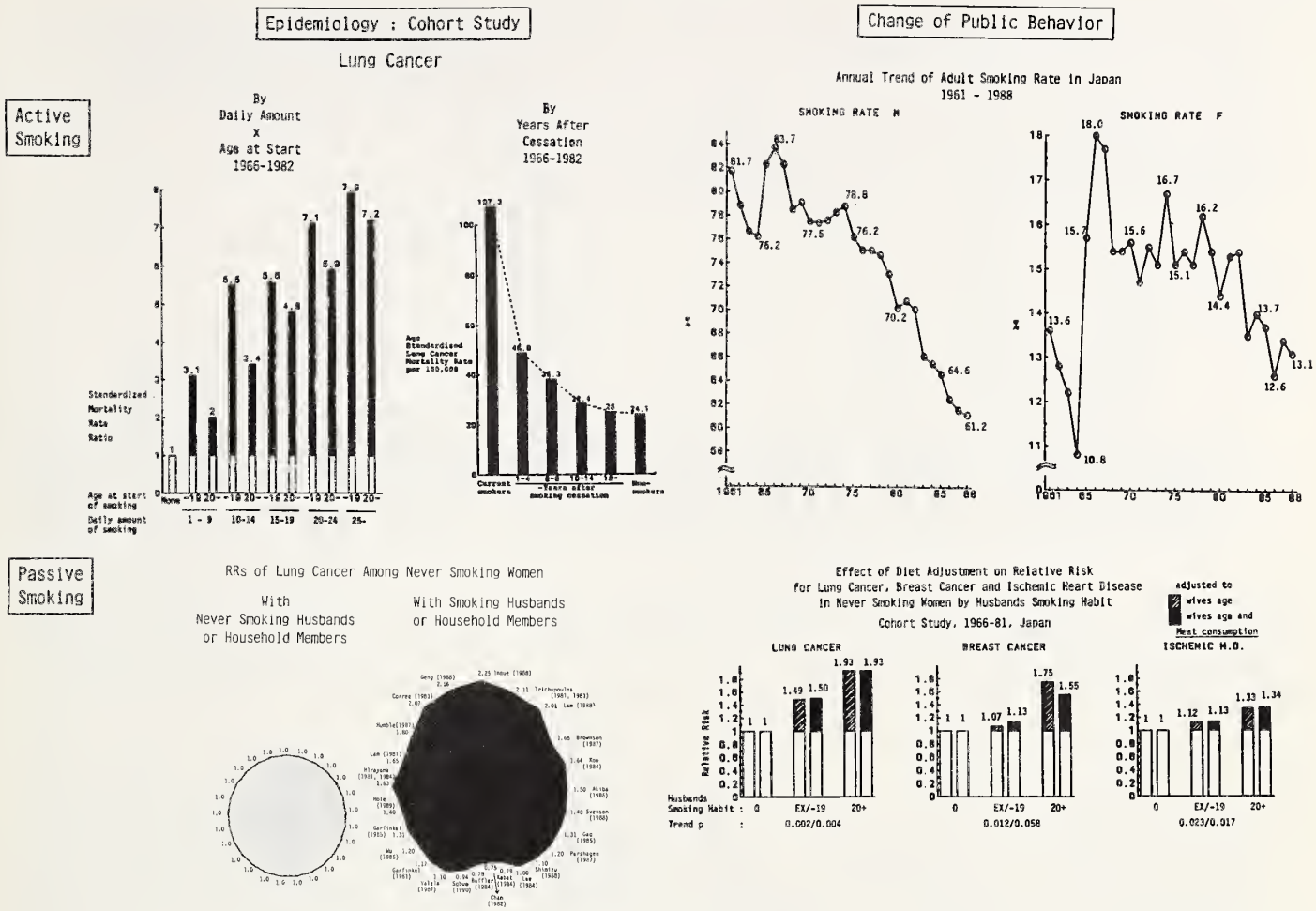



**Figure 5.**—Results of a cohort study on active (*top left*) and passive (*bottom left*) smoking and lung cancer and their effects on public behavior change (*above*).

consumption was associated with elevated risk of cancers at most sites (*1*).

When the evidence that cancer risk is reduced by daily consumption of GYV was reported, the public responded by raising per-capita consumption of GYV over 40% during a short period (8 years; fig. 11). A nationwide opinion survey of 6000 randomly selected individuals conducted by Mainichi Press in 1988 also revealed GYV consumption as the primary "daily practice for cancer prevention," being listed by 74% of women and 53% of men. This is another example of successful implementation of strategies derived from epidemiological research.

### Role of GYV in Modifying Risk

The highest-risk group for cancer includes people who smoke, drink, and consume meat daily but do not consume GYV daily. Those who do the opposite have the lowest risk for cancer (eg, Seventh-Day Adventists). Daily consumption of GYV alone was shown to be effective in reducing the risks of the highest-risk group (fig. 12).

### Fish and Cancer

The role of daily fish consumption should also be studied in depth in view of the significantly lower risk of some cancers in daily fish consumers observed in our large-scale cohort study. The risks for non-, rare, occasional, and daily female consumers of stomach cancer were 1.00, 0.82, 0.72, and 0.67 ($P$ = 0.014) and for cervical cancer were 1.00, 0.72, 0.54, and 0.42 ($P$ = 0.00004), respectively.

## DISCUSSION

Gastric cancer is the most prevalent cancer in Japan. Both correlation and case-control studies showed that the frequent consumption of the highly salted foods traditionally eaten in Japan must be the major risk factor for the disease. Active public education and campaigns advising people to reduce consumption of salty foods, together with the effect of the electric refrigerators introduced into

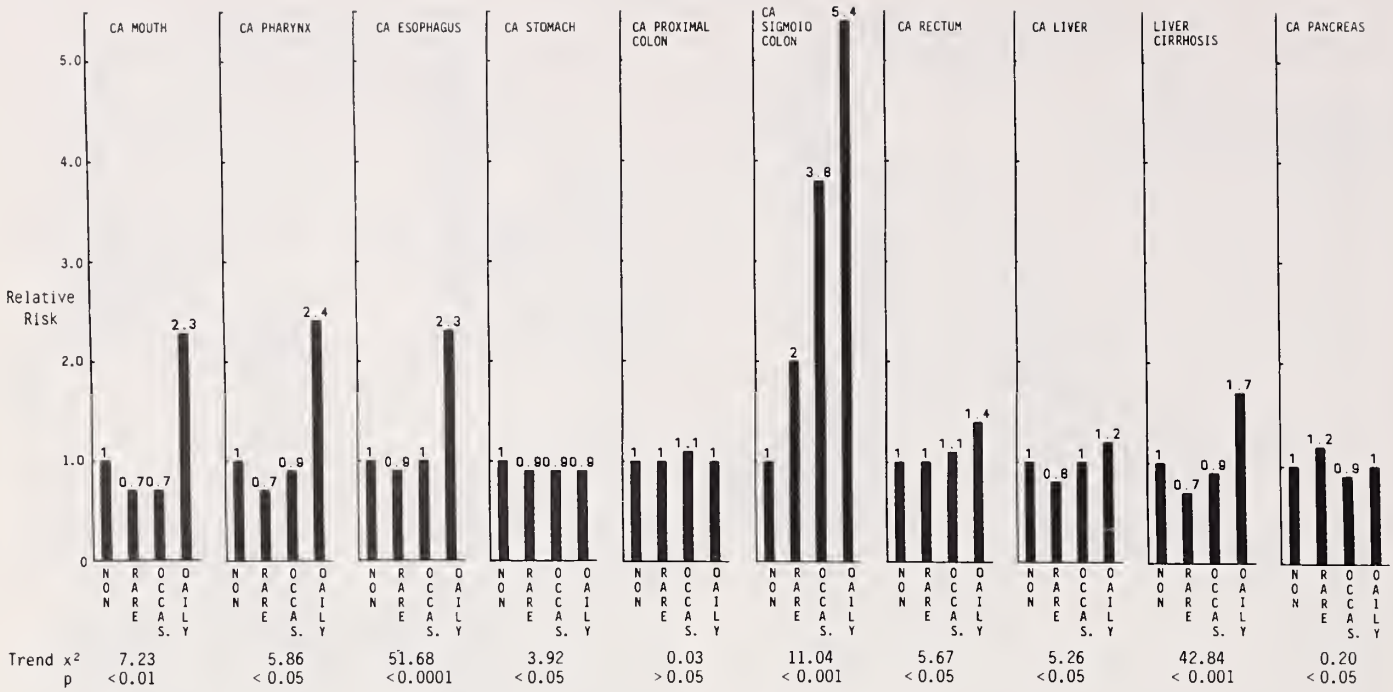



**Figure 6.**—Age-standardized relative risk of cancers (CA) of digestive organs by frequency of alcohol consumption. Cohort study, 1966–1982, Japan (men).

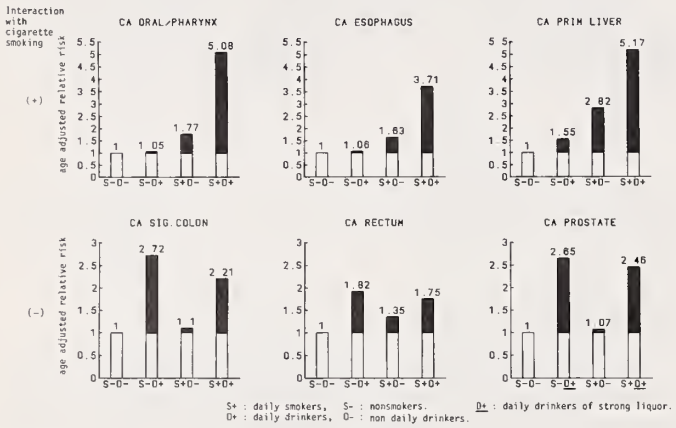



**Figure 7.**—Combined effect of alcohol consumption and cigarette smoking on risk of cancers (CA) of selected sites. Cohort study, 1966–1982, Japan (men).

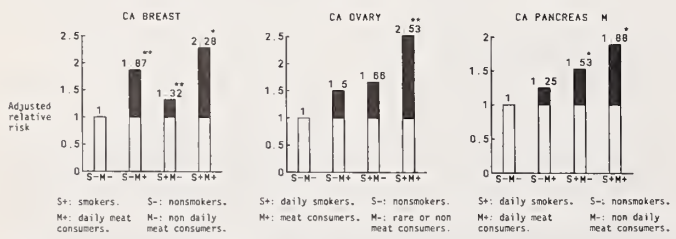



**Figure 8.**—Combined effect of meat consumption and cigarette smoking on risk of cancers (CA) of selected sites. Cohort study, 1966–1982, Japan.

the majority of households in the 1960s, prompted a drastic public behavior change and eventually resulted in a dramatic reduction in gastric cancer mortality in Japan.

Similarly, when results of epidemiological studies on the hazards of both active and passive smoking were repeatedly reported and made public during the past 25 years, the public was motivated to change their behavior. Close associations of lung cancer risk with the number of cigarettes smoked per day, age at initiation of smoking, and years after smoking cessation were in line with reports from Western countries. The effect of passive smoking on lung cancer was first detected in 1981 by our cohort study in Japan, and results of studies conducted thereafter were mostly similar to that of our study. After adjusting the frequency of meat consumption, the observed effect of passive smoking remained almost unchanged for lung and breast cancers and ischemic heart disease. These findings are new in the literature.

A trial to modify public behavior with regard to the hazards of heavy consumption of alcoholic beverages is in progress and includes listing alcohol-related cancers according to presence or absence of interaction with smoking habits. This classification is also new in the literature.

Frequent consumption of high-fat foods was closely associated with the risks of breast, ovarian, and pancreatic cancers, particularly when combined with cigarette smoking. These results not only confirmed the validity of previous reports but also provided new information. A high-

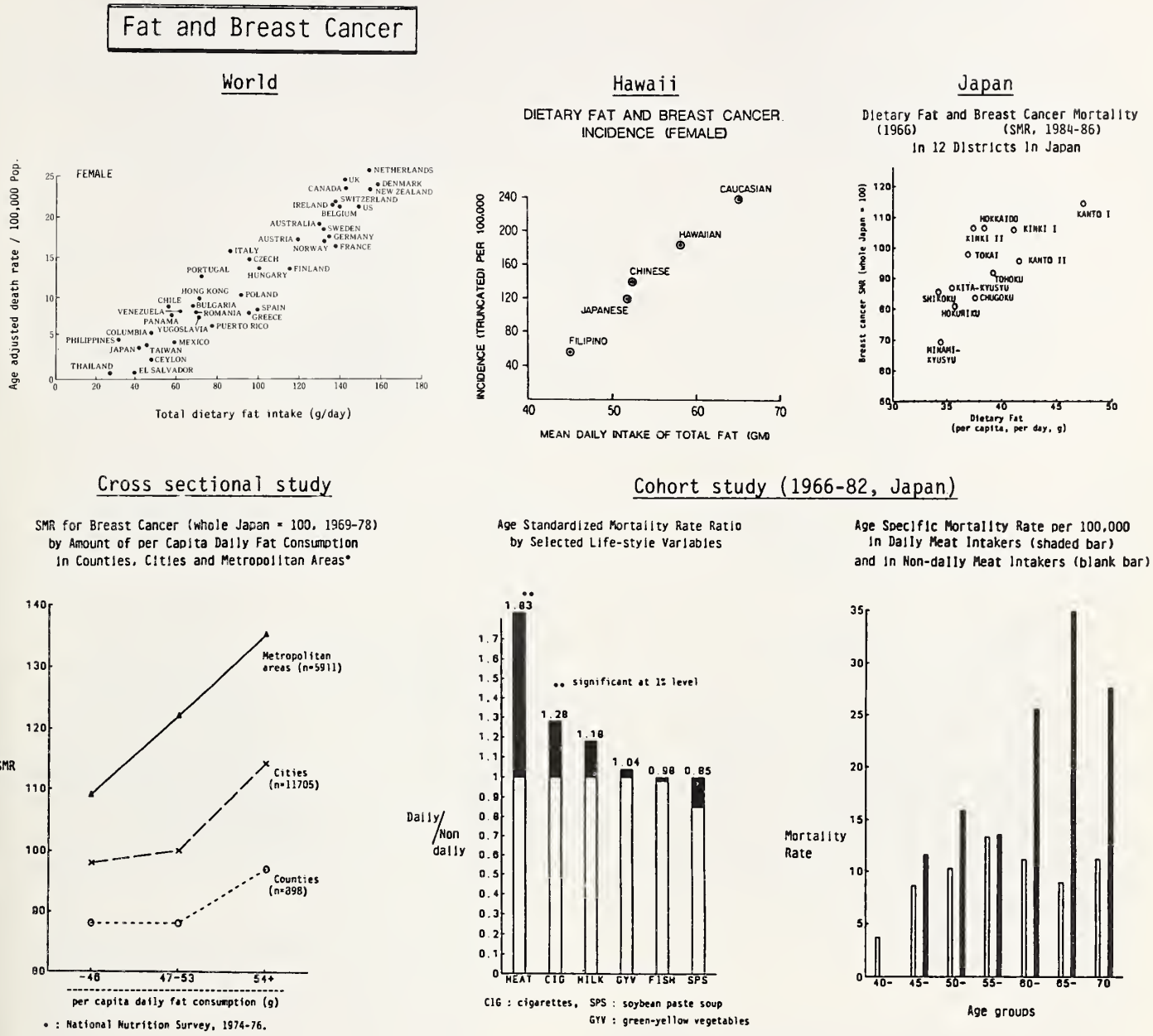



**Figure 9.**—Epidemiological evidence showing association between fat consumption and breast cancer.

fat diet seemed to be the common risk factor for these cancers, and risks were interpreted to become greater when combined with known cancer promoters, eg, cigarette smoking. The dramatic effect of the stabilization of animal-fat intake on breast and colon cancer mortality observed in Japan after 1974, immediately following the first oil crisis, is an example of unintended nationwide dietary intervention against these cancers.

The daily consumption of GYV rich in $\beta$-carotene, vitamin C, minerals, and fibers was shown to commonly lower risks of stomach, colon, lung, cervical, and prostate cancers. The extent of risk reduction for lung and cervical cancers with the increase in frequency of consumption of GYV was most striking in heavy smokers. The antioxidant/antipromoter effect of $\beta$-carotene and other constituents of GYV was particularly visible when exposed to a large amount of oxygen radicals/cancer promoters such as those originated from cigarette smoking. A drastic increase in the consumption of GYV in recent years in Japan strengthens my conviction that results of properly conducted epidemiological studies when they are widely reported to the public can modify public behavior.

Finally, daily fish consumption was noted to lower the risk of cervical and stomach cancers. The beneficial ef-

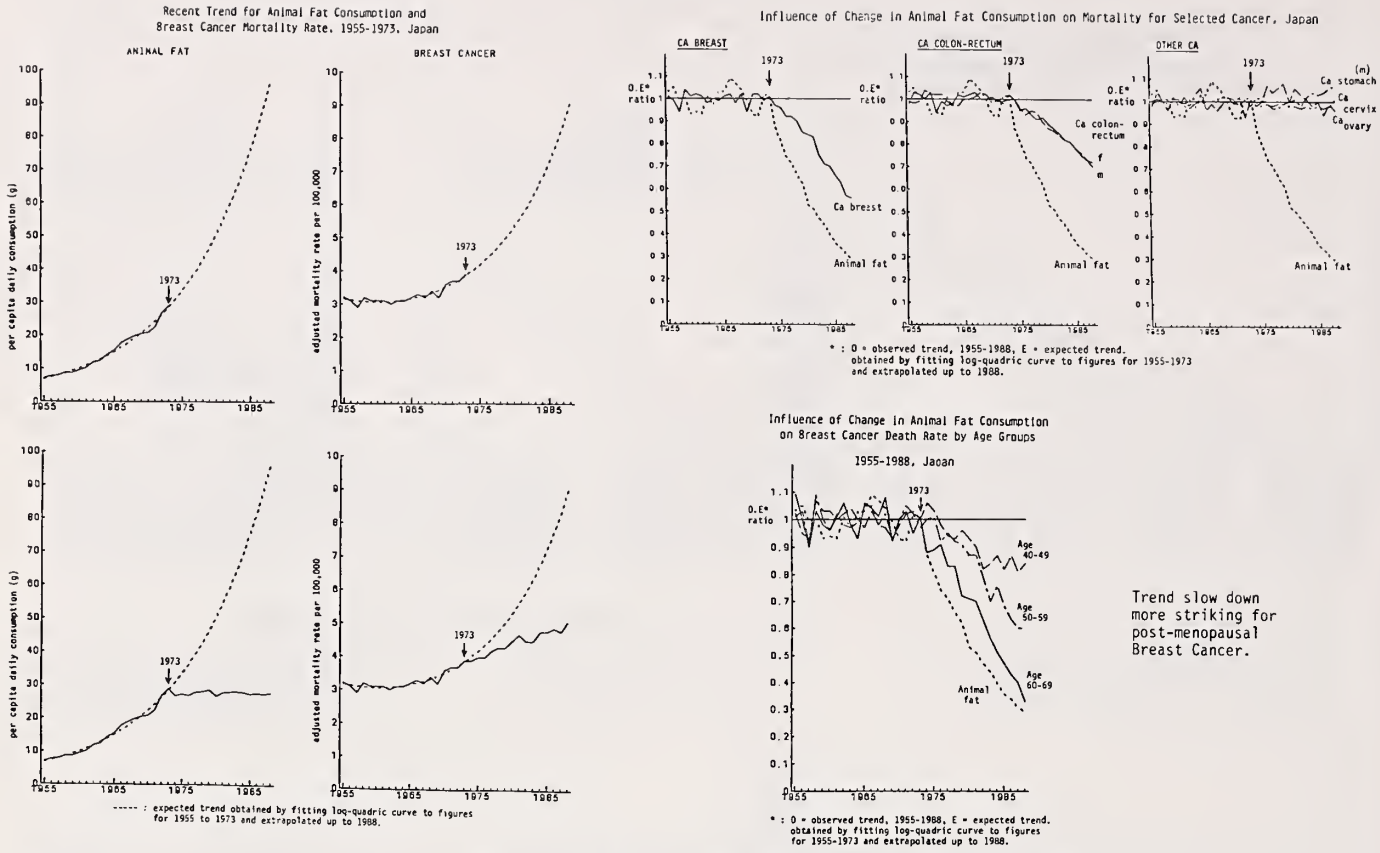



**Figure 10.**—Effect of stabilization of animal-fat consumption on trend of breast and colorectal cancers (CA), Japan.

fects of fish consumption should be studied, including the potential role of ω-3 fatty acids.

These examples obtained in Japan are important in that they show the validity of a scheme of dynamic flow from establishment of epidemiological evidence to public behavior change and eventually to mortality reduction of target cancers (Table 1).

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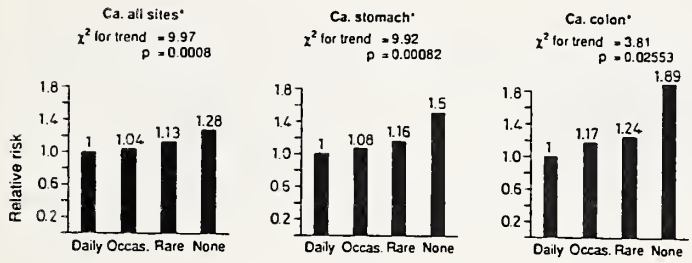
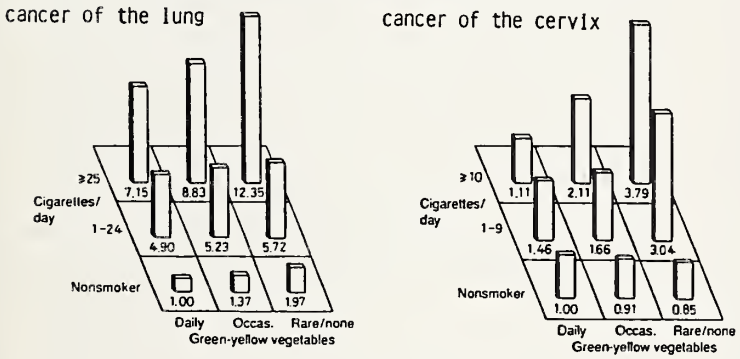
## Green-Yellow Vegetables and Cancer

### Cohort Study

Mortality Rate Ratio for Cancer of Selected Sites
by Frequency of Green-Yellow Vegetables Consumption
Cohort Study, 1966-82, Japan

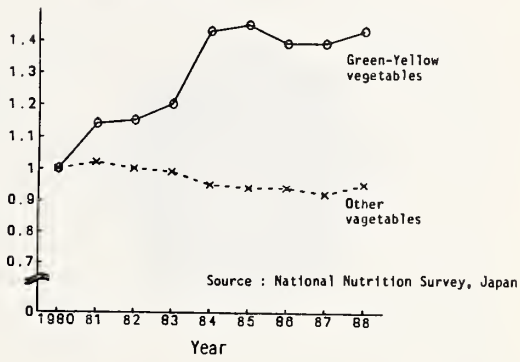



Relative Risks by Frequency of Consumption of
Green-Yellow Vegetables and Number of Cigarettes per Day

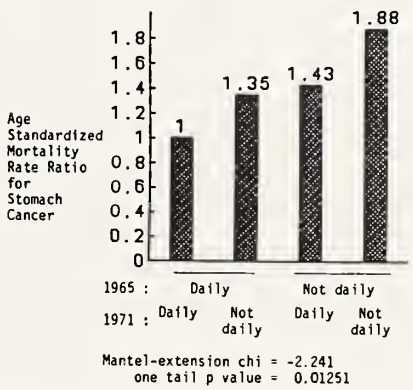



### Change of Public Behavior

Annual Trend of Per Capita
Daily Consumption of Vegetables in Japan
1980-88 (1980=1.00)




Effect of Change in Frequency
of Green-Yellow Vegetables Consumption
on Subsequent Mortality Ratio
for Stomach Cancer (age standardized)
Cohort Study, 1966-82, Japan (Males)




Mantel-extension chi = -2.241
one tail p value = 0.01251

**Figure 11.**—Results of cohort study on green-yellow vegetables (*left*) and cancer of selected sites and their effects on public behavior change (*right*).

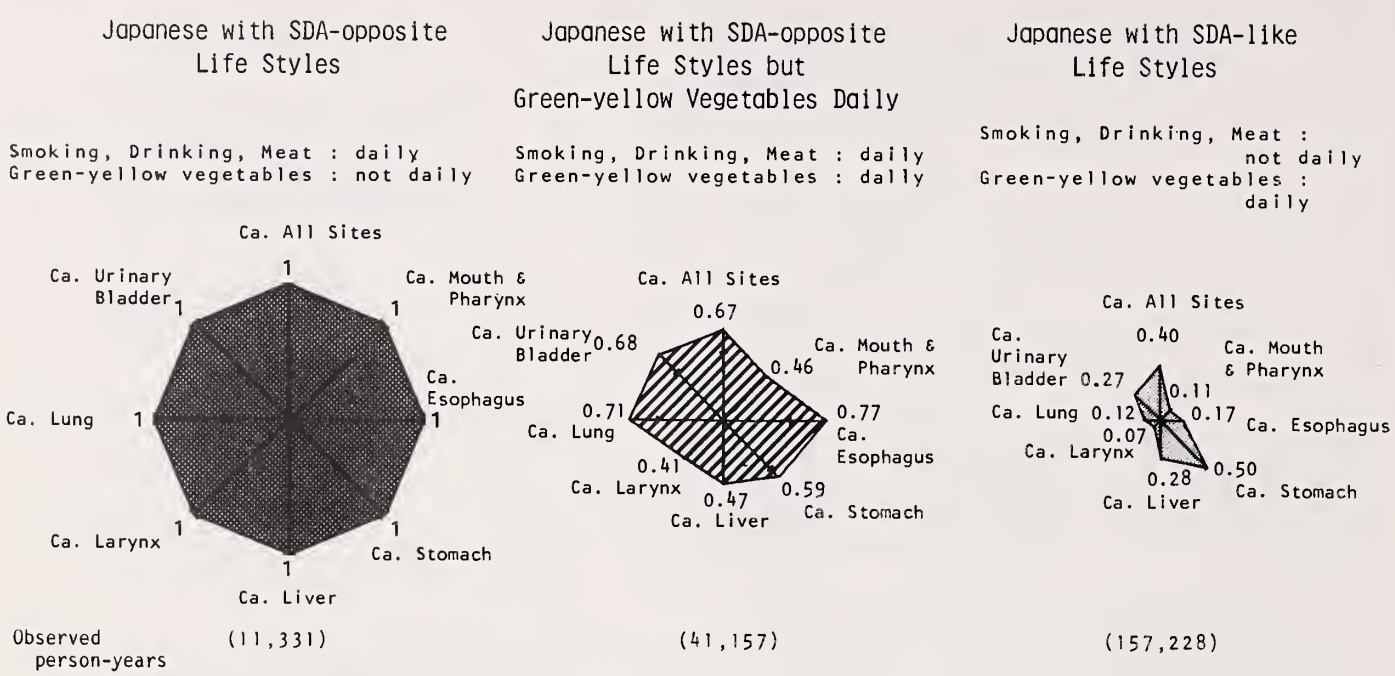



**Figure 12.**—Cancer (Ca) risk in Japanese with different life-styles (SDA = Seventh-Day Adventists). Cohort study, 1966–1981, Japan.

**Table 1.**—Promising changes in selected life-styles in Japan

| Behavior | 1966 | 1988 | Change, % |
|---|---|---|---|
| Adult smoking rate,* % | | | |
| Male | 83.7 | 61.6† | −27 |
| Female | 19.0 | 12.7† | −29 |
| Salt intake,‡ g | 14.5§ | 12.2 | −16 |
| Animal-fat intake,‡ g | 27.0‖ | 28.0 | 0 |
| Green-yellow vegetable intake,‡ g | 45.7 | 72.8 | +59 |

*Data from Japan Tobacco and Salt Public Corporation and Japan Tobacco Industry.
† 1989.
‡Data from National Nutrition Survey, Ministry of Health and Welfare, Japan.
§ 1971.
‖ 1972.

# Diet Modification and Gastric Cancer Prevention[1]

Pelayo Correa[2]

**ABSTRACT—The relative strengths of the etiologic factors identified for gastric cancer are discussed. On the basis of available scientific data, it is recommended that dietary prevention of gastric cancer be based on attempts to reduce the ingestion of foods with a high content of salt and to increase the intake of fresh fruits and vegetables. Other identified etiologic factors offer promise and are being investigated but do not yet justify recommendation to the general public. [J Natl Cancer Inst Monogr 12:75–78, 1992]**

Gastric cancer is no longer one of the major cancer problems in the United States, but it is certainly a major international health problem. As of 1980, gastric cancer was the most frequent malignant disease, excluding skin cancer, in the world, with 669 400 new cases per year (*1*). The incidence of lung cancer has been increasing worldwide and probably has surpassed gastric cancer in recent years.

The general decline of gastric cancer rates in most developed countries overshadows the fact that there are groups at high risk in most populations. In the United States, high rates are found in American Indians, blacks, and immigrants from Latin America, Asia, and northern Europe (*2*).

The reasons for the decline in gastric cancer rates are not well understood, but most investigators find changes in the diet precede the decline (*3*). Even though the length of the gastric precancerous state is measured in decades, dietary changes can affect cancer rates in a short period. The gradual decline in cancer rates in European countries was temporarily interrupted immediately after the Second World War, apparently reflecting dietary changes (*4*).

## CAUSES OF GASTRIC CANCER

Two main types of gastric carcinoma have independent epidemiological characteristics. The most common type in populations at high risk has been called the intestinal type because it resembles intestinal carcinomas and usually arises in areas of the mucosa that have previously become intestinalized. It is also the type that has been decreasing in frequency most markedly in industrialized countries, and because of that trend, it has also been called the epidemic type. The other common type has been called diffuse, infiltrative, or poorly differentiated. This type is predominant in populations at low risk and is becoming relatively more frequent in populations with marked declines in the intestinal type.

The intestinal type of carcinoma is considered the result of a prolonged precancerous process in which the following lesions appear to develop in a sequential manner: superficial gastritis, atrophy, small-intestinal metaplasia, colonic metaplasia, dysplasia, and, finally, invasive carcinoma (*5*). The components of the precancerous process constitute the nosologic complex whose basic element is the multifocal atrophic gastritis, whose prevalence is high in populations at high risk. Investigators from different scientific disciplines working in different countries have identified risk factors for gastric cancer that have led to the postulation of an etiologic hypothesis (*5*). Several etiologic agents have been recognized as acting at different points of the chain of causation. The first step of the process, characterized by active inflammation, has been linked to two factors: excessive consumption of salty foods and infection with *Helicobacter pylori*. Excessive salt is probably the most consistent and better-documented etiologic factor for gastric carcinoma. A positive international correlation between salt intake and gastric cancer mortality has been reported (*6*). The first case-control study showing increased relative risk associated with the intake of salty foods was reported in Japan (*7*). More recent case-control studies showing excessive risk associated with salt intake are shown in table 1.

Excessive salt in the diet of experimental rats increases cell replication, a factor known to increase susceptibility to carcinogens (*8*). Feeding highly salted rice to mice results in glandular atrophy, a cancer precursor in humans (*9*). Excessive salt added to the diet of experimental rats receiving the gastric carcinogen *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) causes marked potentiation of carcinogenesis (*10*). Excessive salt has met many epidemiological and experimental requirements for a gastric cancer etiologic factor. Lower salt intake is probably causally related to the declining gastric cancer rates observed in many countries.

A consistent finding in studies of the analytical epidemiology of gastric cancer has been the protective role of fresh fruits and vegetables (table 2). Two general mechanisms of inhibition or retardation of the gastric carcinogenic process are being actively investigated. One involves vitamin C, which has the double role of blocking the intragastric synthesis of *N*-nitroso carcinogens and of retarding the progression of transformed cell clones through

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Table 1.—Case-control studies of stomach cancer: risk associated with dietary salt

| Reference | Relative risk |
|---|---|
| Japan, 1985, Tajima and Tominaga (*26*) | 1.99 |
| New Orleans, LA, blacks, 1985, Correa et al. (*27*) | 1.75 (NS) |
| China, 1988, You et al. (*28*) | 1.4 |
| Italy, 1990, Buiatti et al. (*29*) | 1.4 |
| Los Angeles, CA, 1990, Wu-Williams et al. (*30*) | 2.2 |
| Buffalo, NY, 1990, Graham et al. (*31*) (sodium) | 3.09 |

Table 2.—Case-control studies of stomach cancer: relative risk associated with high intake of fresh fruits and vegetables

| Reference | Fresh vegetables | Fresh fruits |
|---|---|---|
| Canada, 1985, Risch et al. (32) | 0.84 | 0.75 (citric) |
| Greece, 1985, Trichopoulos et al. (33) | 0.70 | 0.37 (NS) |
| New Orleans, LA, blacks, 1985, Correa et al. (27) | 0.50 | 0.33 |
| Poland, 1986, Jedrychowski et al. (34) | 0.45 | 0.28 |
| Italy, 1987, LaVecchia et al. (35) | 0.61 | 0.51 (citric) |
| China, 1988, You et al. (28) | 0.4 | 0.6 |
| Italy, 1990, Buiatti et al. (29) | 0.6 | 0.4 |

fibroplasia. The first role is based on the destruction of the nitrite molecules (*11*). It has been reported that only the reduced form of vitamin C (ascorbic acid) is capable of reacting with and inactivating the nitrite molecules. The oxidized form of vitamin C (dehydroascorbic acid) has no such activity (*12*). This observation may explain why vitamin C is considered a risk factor for stomach cancer in some populations but not in others. Ascorbic acid is actively concentrated by the gastric mucosa from the blood and secreted into the gastric cavity (*13*). No clear explanation is available for this peculiar function, but it suggests that the antioxidant role of ascorbic acid may be involved in detoxification of luminal carcinogens. Note that infection with *H. pylori* blocks the secretion of ascorbic acid (*14*). This bacterium has been implicated as a risk factor in gastric carcinogenesis (*15*, *16*), and findings suggest an interaction between infection and nutrition in the carcinogenesis process (*5*).

The other postulated mechanism of inhibition of gastric carcinogenesis is mediated through β-carotene and related compounds. Blood levels of carotenoids are remarkably low in patients with dysplasia in the population of Nariño, Colombia (*17*). β-Carotene and its related pigment canthaxanthin (which is not a precursor of vitamin A) greatly inhibit experimental gastric carcinoma (but not early precursors) in rats receiving MNNG (*18*). The above reports suggest that β-carotene acts in the late stages of carcinogenesis. β-Carotene may act as a scavenger of free radicals (*19*) and increase cell-to-cell communications through the widening of intercellular gap-junction channels. The expression of malignant phenotypes is inhibited in transformed cells connected to nontransformed cells through such junction channels (*20*). This phenomenon may be especially relevant in the gastric mucosa, where neighboring transformed and nontransformed cells are frequently found.

## PREVENTION

Primary prevention of gastric carcinoma should be based on the control of the etiologic agents. Avoiding salty foods should be a major concern in primary prevention. Some calcium salts, especially calcium lactate, may block some of the damaging effect of high sodium intake (*21*). Adequate consumption of fresh fruits and vegetables provides sufficient amounts of reduced ascorbic acid and β-carotene, strongly suspected to play a protective role. The same foods contain various nonnutrients that inhibit carcinogenesis (*22*). The control of *Helicobacter* infections, especially when associated with severe gastritis, should be considered, but its beneficial effects are still under investigation.

Secondary prevention of gastric carcinoma has a role in patients suspected to be at high risk because of advanced premalignant lesions such as dysplasia and, probably, colonic metaplasia, Frequent endoscopies should be done to detect superficial carcinomas (early cancer in the Japanese nomenclature), which have an excellent prognosis after surgery.

The treatment of dysplasia (and of colonie metaplasia) is still controversial. The natural history of such lesions, especially the time required for transformation into invasive carcinoma, is poorly understood. Chemoprevention trials with antioxidants, anti-*Helicobacter* therapy, calcium salts, and dietary modifications are being proposed and might shed some light in this field. Markers of increased risk are provided by pepsinogen I and pepsinogen I/II ratios in the blood. Very low levels have been found in some populations to be good indicators of increased risk. They could be used to identify appropriate high-risk participants for chemoprevention trials and to monitor their outcomes (*23*).

## CONCLUSIONS

The accumulated evidence appears sufficient to classify frequent intake of salty foods and inadequate intake of fresh fruits and vegetables as epidemiological factors in the causation of gastric cancer. These two dietary items have demonstrated consistency, biological plausibility, strength, and correct temporality in relation to gastric cancer risk. These factors should therefore be the basis for prevention campaigns in populations at high risk. Dietary modifications to reduce salt and increase fresh fruit and vegetable intake will probably also be beneficial in the prevention of other cancers and chronic diseases. All pop-

ulations may benefit from dietary recommendations of this type, which have not been adequately emphasized.

The mechanisms of the beneficial effects of fresh fruits and vegetables are not well understood. They contain numerous nutrient and nonnutrient antioxidants that may be involved in anticarcinogenesis. Some such antioxidants, ie, ascorbic acid, $\beta$-carotene, and $\alpha$-tocopherol, are harmless and could be used in cancer prevention. Because of scientific uncertainties, however, these antioxidants fall more appropriately in the category of maybes. Another member of this category would be *H. pylori*.

Other factors have been suggested in the etiology of gastric cancer and should be considered rumors. Excessive intake of nitrates may be a factor in people who have chronic atrophic gastritis, because in these individuals, excessive nitrite is produced in the gastric cavity; excessive nitrite may be a precursor of nitrosamine and other carcinogenic compounds. Tobacco and alcohol increase gastric cancer risk in some populations, but the findings lack consistency and strength. Genetic susceptibility is probably a modulating factor in gastric carcinogenesis, but its determinants are poorly understood (*25*, *26*).

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# Cancers Associated With High-Fat Diets[1]

Carlo La Vecchia[2-4]

**ABSTRACT—The association between fat intake and several common cancers, eg, those of the colorectum, breast, endometrium, ovary, and prostate, received its strongest support from correlation studies on populations. On an international scale, strong direct correlations were observed between fat intake and incidence or mortality from these neoplasms; several correlations were also observed on a national level and persisted after allowance for major identified covariates. Further support came from the observation of change in rates in migrant groups. This association, however, has been described as being weak in individuals as opposed to populations. Briefly, diets high in fat (and meat) have been associated with high risk of colorectal cancer in several case-control studies, with saturated fat being specifically implicated. However, the strength of the association is generally moderate, and a few disparities have to be considered. In relation to breast cancer, several case-control studies have reported associations with total fat, and there was some indication that the associations might be stronger for saturated fat. These relationships, however, were weak and inconsistent in various studies. Thus, a plausible conclusion from case-control studies is that there is indeed some association between fats and breast cancer risk, which is, however, limited and, hence, extremely difficult to prove in epidemiological terms. To further complicate the issue, the results of cohort studies do not support the association. Data from analytical studies are more limited for endometrial, ovarian, and prostate cancers, but, again, seem to indicate a possible relationship with diets high in fat. It is, nonetheless, disappointing that information on fats and the risk of those common neoplasms is still so imprecise, and, hence, that indications for prevention are largely open to debate. [J Natl Cancer Inst Monogr 12:79-85, 1992]**

The association between fat intake and several common cancers, eg, those of the colorectum, breast, endometrium, ovary, and prostate, has received its strongest support from correlation studies on populations. On an international scale, strong direct correlations have been observed between breast cancer mortality in various countries and fat consumption (*1*). Armstrong and Doll (*2*) systematically reviewed incidence rates in 23 countries and mortality rates in 32 countries and found coefficients above 0.6 for mortality and above 0.5 for incidence for fat intake and cancers of the colorectum, breast, corpus uteri, and ovary; for prostatic cancer mortality, the correlation coefficient was 0.7.

In a more recent international comparison of mortality rates for cancer of the breast, ovary, prostate, and colon and the consumption of various fats, Rose et al. (*3*) confirmed the strong positive correlations between these four cancer sites and total animal-fat intake (but to a lesser extent with total vegetable-fat intake, particularly in countries where olive oil is the main source of fat). With reference to specific fats, strong positive correlations were evident for meats and milk in relation to breast cancer, milk for prostate and ovarian cancers, and meat for colon cancer.

Similar correlations were observed on a national level in Italy and persisted after allowance for major identified covariates. Table 1 gives, as an example, the crude and partial correlation coefficients between selected food items and breast cancer rates in various regions of Italy, a country with marked differences in dietary habits and cancer rates. Foods rich in animal fats were positively correlated with breast cancer mortality, and the coefficients remained significantly positive after allowance for the women's ages at birth of first offspring (*4*).

Inspection of the geographic differences in mortality from cancers of the colon (fig. 1) or breast (fig. 2) in different areas of Italy with substantial variability in diet composition suggests that type of fat, in addition to total fat intake, may be of relevance. In northern Italy, where colon and breast cancer rates are uniformly elevated, butter is the main type of seasoning fat; in southern Italy, olive oil is most commonly used (*5*).

Further support to the hypothesis that dietary fat may be relevant to the risk of several common cancers comes from studies of migrant peoples. Colorectal cancer, for instance, is extremely rare in black populations of West Africa, but is similar in black and white Americans; the rate of prostate cancer in Hawaiian Japanese is between that of Japanese residents and the white population of Hawaii (*6*).

Observational studies on populations are useful for formulating hypotheses, but they cannot provide convincing

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[4] I thank Judy Baggot and Hanne-Christine Janin for editorial assistance.

Table 1.—Correlation between breast cancer mortality and selected dietary variables in various Italian regions

| Food items | Correlation coefficients | |
|---|---|---|
| | Crude | Adjusted for age at first birth |
| Milk | 0.81 | 0.52 |
| Cheese | 0.74 | 0.52 |
| Meat | 0.39 | −0.25 |
| Sugar | 0.66 | 0.15 |
| Wine | 0.37 | −0.45 |
| Pasta | −0.78 | −0.31 |

From (*4*).

evidence of cause-effect relationships. Unfortunately, however, the evidence from analytic epidemiological studies is much less convincing, and the correlation between fat intake and cancer incidence has been described as weak in individuals when compared with populations.

## COLORECTAL CANCER

Diets rich in fat (and particularly meat) have been associated with high colorectal cancer risk in several case-control studies. In some studies that specifically considered cancer and types of fats, positive associations were found with saturated fats. Diets rich in vegetables, fruits, and possibly fiber tended to be associated with a low risk of cancer (*7–13*). Two cohort studies have been published on diet and colon cancer, and both found positive associations with fat (*14*, *15*).

A high-fat diet may induce colorectal carcinogenesis by increasing synthesis and secretion of cholesterol and bile acids. These are converted by colonic bacteria to secondary bile acids, which may promote tumors. Whereas saturated and unsaturated fats have similar effects on bile acid and its synthesis (*16*), it has been suggested that the promotional effect may be less for monounsaturated fats.

Although the overall pattern from case-control studies on the relation of dietary composition to elevated colorectal cancer risk is fairly consistent, the strength of the association with fats is generally moderate. Table 2 gives, as an example, the relative risk estimates for various fat-rich foods from an Italian case-control study (*11*) and those for various types of fats in a study conducted on Chinese in North America and China (*13*). Most of the relative risk estimates were between 1 and 2, and some inconsistencies were apparent either for various intestinal subsites or between the sexes.

Reasons for these inconsistencies are not obvious, but two at least merit careful consideration: difficulties in collecting dietary information and heterogeneity in fat intake between and within various populations. Any dietary measurement instrument is imprecise, the composition of fat intake in diet is difficult to assess, and it is even more difficult to make allowance for a measure of total caloric intake (*17*). On a population level, the difficulties may seem less important, but they are certainly still

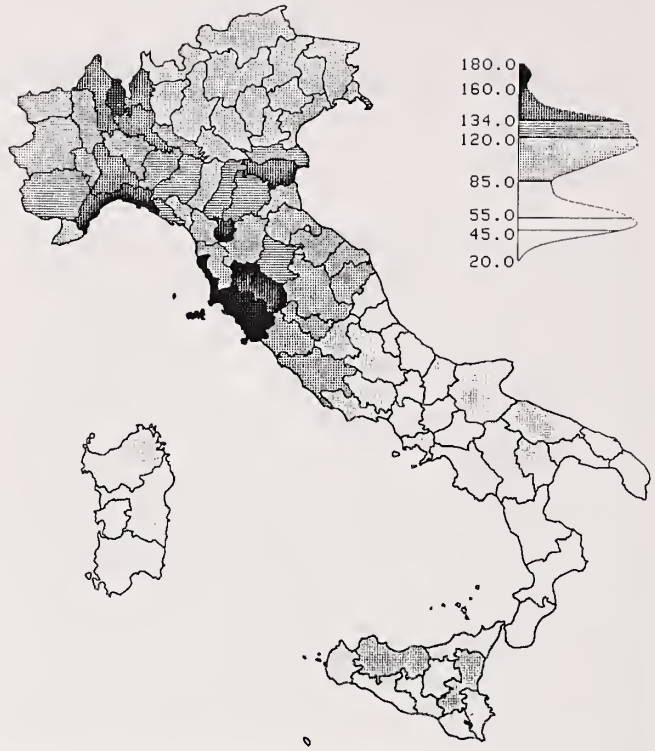


Figure 1.—Colon cancer mortality in Italian men.

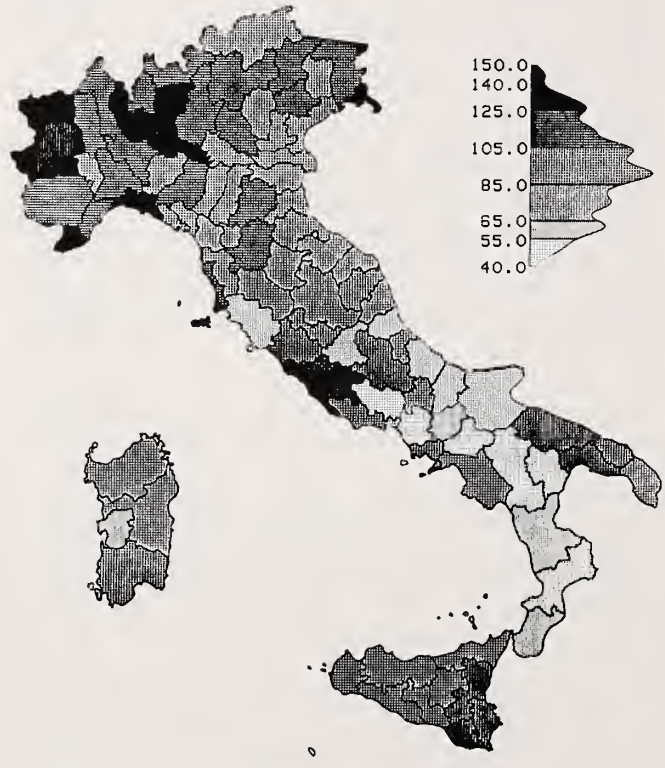


Figure 2.—Breast cancer mortality in Italian women.

**Table 2.**—Relationship between measures of fat intake and colorectal cancer risk in selected populations

| Study, source, and type of fat | Relative risk for highest vs. lowest consumption level | |
|---|---|---|
| | Colon cancer | Rectal cancer |
| La Vecchia et al., Italy, 1988 (*11*) | | |
| Butter | 2.0 | 1.7 |
| Margarine | 0.9 | 1.5 |
| Olive oil | 1.9 | 1.3 |
| Other oils | 0.8 | 0.8 |
| Meat | 2.0 | 2.2 |
| Whittemore et al., North American Chinese, 1990 (*13*) | | |
| Saturated fat | | |
| Men | 1.8 | 2.4 |
| Women | 2.0 | 2.9 |
| Unsaturated fat, men | 0.9 | 0.8 |
| Whittemore et al., China, (*13*) | | |
| Saturated fat | | |
| Men | 1.2 | 1.1 |
| Women | 1.1 | 1.6 |
| Unsaturated fat | | |
| Men | 1.0 | 1.0 |
| Women | 1.0 | 0.8 |

may seem less important, but they are certainly still present because disappearance statistics include both intake and waste, which vary from one population to another and tend to be systematically greater in wealthier countries, where fat intake is generally higher (*18*).

In relation to the variability of dietary patterns, for any dietary component there is no unexposed category (as, for example, for smoking), and, in principle, associations are more difficult to assess in situations in which dietary heterogeneity is smaller. These and other difficulties do not totally eclipse the evidence of an association between fat and colorectal cancer in humans, although they impede a precise assessment of the association in quantitative terms.

## BREAST CANCER

As with colorectal cancer, most of the initial evidence linking breast cancer to diet has been derived from animal experiments and from ecological studies on diet and breast cancer risk in different populations. Unfortunately, the evidence from analytical epidemiology to date is largely confusing. Case-control studies have reported associations with fats and specific food items (eg, fried foods, dairy products, beef and other red meat, pork, and desserts) (*19–30*). The associations, however, were moderate and inconsistent. Published evidence from case-control studies is summarized in table 3. Some studies found a direct association with fats, such as those from Canada (*20*), Israel (*26*), and the Netherlands (*25*); in an Italian study, the relative risk for the largest saturated fat intake recorded was 2.8 (*28*). In other studies the association was weak and inconsistent, although the point estimates were above 1 (*20*, *21*, *24*, *25*, *29*), whereas studies from the United States (*22*), Greece (*23*), Japan (*27*), and Australia (*30*) showed no evidence of a positive association. To further complicate the issue, three prospective US studies (*31–33*) found no evidence of any positive association with total fat intake or with any specific type of fat.

Thus, the relationship between fat and breast cancer remains even more obscure and uncertain than that for colorectal cancer. It is possible that there is no real association between adult fat intake and breast cancer risk, whereas diet in childhood and adolescence may (as suggested by migrant studies) or may not be associated with subsequent breast cancer risk. Even if the increased risk for the upper levels of fat intake were on the order of 1.3–1.5, as has been found in most case-control (but not prospective) investigations, this would represent an association of magnitude similar to that observed for most established reproductive and hormonal breast cancer risk factors (*34*) and would have major public health and preventive implications.

## ENDOMETRIAL AND OVARIAN CANCERS

Although strong positive correlations have been observed between fats and oils and endometrial cancer incidence, the issue is clearly complicated by the close correlation between fat and energy intake, the major determinant of obesity and a consistently recognized risk factor for endometrial cancer.

Few analytical studies have directly addressed the role of diet in the etiology of endometrial cancer. Preliminary results from a case-control study based on 24-hour recall suggested that intake of carbohydrates and total calories

**Table 3.**—Relation of total fat* intake and breast cancer risk in selected case-control studies

| Study and source | Level of fat intake† | | | | |
|---|---|---|---|---|---|
| | 1‡ | 2 | 3 | 4 | 5 |
| Phillips, 1975 (*19*) | 1 | 1.2 | — | — | — |
| Miller et al., 1978 (*20*) | 1 | 1.7 | 1.2 | 1.8 | — |
| Lubin et al., 1981 (*21*) | 1 | 1.6 | 1.5 | 1.8 | — |
| Graham et al. (*22*) | 1 | 1.1 | 1.2 | 0.9 | — |
| La Vecchia et al., 1987 (*24*) | 1 | 1.3 | 1.3 | — | — |
| Hirohata et al., 1987§ (*27*) | | | | | |
| Japanese | 1 | 1.1 | 1.0 | 1.3 | — |
| White | 1 | 0.7 | 0.5 | 0.8 | — |
| Katsouyanni et al., 1988‖ (*23*) | 1 | 1.4 | — | — | — |
| Rohan et al., 1988 (*30*) | 1 | 0.9 | 1.1 | 1.1 | 0.9 |
| Toniolo et al., 1989 (*28*) | 1 | 1.9 | 1.6 | 1.8 | — |
| Iscovich et al., 1989 (*29*) | 1 | 1.4 | 0.7 | 3.6 | — |
| Van't Veer et al., 1990 (*25*) | 1 | 1.5 | 1.6 | 1.3 | 2.6 |

*Animal fat, when it is the only fat available.
†As reported in original studies. Thus, data in this table allow within- but not between-study comparisons.
‡Reference category.
§Studies based on separate Japanese and white populations.
‖90th vs. 10th centiles.

(but not proteins or fats) was higher in cancer patients than in control subjects (*35*).

A study from Italy, now updated to include a total of 567 cancer patients and 2113 control subjects, reported strong direct associations with subjective intake scores for fats and oils (table 4) and significant protection by green vegetables and fresh fruit (*36*). However, information on only a few food items was collected in that study, and it was not possible to allow for total energy intake. There is, therefore, ample scope for further research on the question of diet and endometrial cancer. In particular, considering that although the risk factors for cancer of the corpus uteri are better defined than those for breast cancer, they cannot by themselves explain the 30-fold difference in incidence rates among various registration areas in the world (*37*).

As for endometrial cancer, most of the links between diet and ovarian cancer are indirect and are based on international differences or correlational studies. Correlations with fats are similar to those for endometrial cancer, although these correlations are somewhat weaker in relation to incidence.

Information from follow-up studies is scanty and controversial. In a cohort of British nuns who had low intake of meat and fats, no reduction in risk was apparent (*38*). Population studies of Seventh-Day Adventists (*39*) or Mormons (*40*) are not very informative, because they differ in several aspects linked to ovarian cancer.

The findings of case-control studies are somewhat more consistent. Among five studies that considered various measures of fat intake, three found significant direct associations (*41–45*; table 5). In one study, based on a Chinese population with wide ranges of consumption of various nutrients that could provide estimates of intake for several nutrients, the effect of fat persisted after adjustment for total calories, whereas no significant association persisted for calories or proteins after allowance for animal-fat intake (*44*).

As for breast cancer, the range of relative risk shown in table 5 is comparable to that of the best recognized hormonal and reproductive risk factors for ovarian cancer. If there is actually a causal association, this could have appreciable public health relevance in developed countries (*37*).

**Table 4.**—Relationship between level of fat intake and endometrial cancer risk, Milan, 1983–1990

| Total fat-intake subjective score | Endometrial cancer patients | Control subjects | Relative risk (95% CI)* |
|---|---|---|---|
| Low | 262 | 1134 | 1† |
| Intermediate | 196 | 708 | 1.2 (0.9–1.4) |
| High | 109 | 271 | 1.8 (1.4–2.3) |
| *P* (trend) | 567 | 2113 | <0.01 |

*Mantel-Haenszel estimates adjusted for age; CI, confidence interval.

†Reference category.

**Table 5.**—Fats and ovarian cancer: summary results from case-control studies

| Study and source | Level of fat intake 1* | 2 | 3 | 4 |
|---|---|---|---|---|
| Byers et al., 1983 (*41*) | 1 | 1.3 | 1.2 | — |
| Cramer et al., 1984 (*42*) | 1 | 1.1 | 1.9 | 1.8 |
| La Vecchia et al., 1987 (*43*) | 1 | 1.2 | 2.1 | — |
| Shu et al., 1989 (*44*) | 1 | 1.1 | 1.8 | 1.9 |
| Slattery et al., 1989 (*45*) | 1 | 0.9 | 1.3 | — |

*Reference category.

## PROSTATE CANCER

There is some indication that animal-fat intake, particularly from milk and dairy products, is related to prostate cancer. In a cohort study of Seventh-Day Adventists, for instance, the relative risk was 1.8 for 1–2 glasses of milk per day and 2.4 for 3 glasses or more, compared with the relative risk for less than 1 glass per day (*46*). In the same study, there was a significant risk associated with heavy intake of cheese, eggs, and meat. In a case-control study from California and Illinois, more cheese and cream were consumed by cancer patients in both areas (*47*), and another case-control study from Minnesota suggested an elevated risk in the highest ice cream consumption category (*48*).

Two case-control studies from northern Italy found elevated risks for milk and/or dairy-product consumption (*49*, *50*). A more detailed investigation from the Roswell Park Memorial Institute found a trend toward a higher risk for intake of fat from meats and a strong direct association with whole milk (relative risk was 2.5 for $\geq 3$ glasses/day) but not with skimmed milk (*51*). This again was interpreted as supporting the hypothesis that animal fat is related to increased prostate cancer risk. The results of selected case-control studies considering the relationship between fats and prostate cancer are given in table 6 (*51–55*). Although the interpretation of most single studies may be open to debate, the overall pattern is consistent with an elevated risk for highest levels of fat intake.

As for endometrial and ovarian cancer, however, limited adequate epidemiological information is available on the role of each specific type of fat on prostatic cancer risk, after allowance for other nutrients. This scanty epidemiological knowledge in relation to fat and other possible causes of prostate cancer is particularly regrettable, because this is one of the most common tumors in men in any developed country. However, few studies of good quality are available.

**Table 6.**—Fats and prostate cancer: summary results from selected case-control studies

| Study and source | Age-group (y) or race | Level of fat intake* | | | | |
|---|---|---|---|---|---|---|
| | | 1† | 2 | 3 | 4 | 5 |
| Graham et al., 1983 (*52*) | <70 | 1 | 1.0 | 0.8 | 0.9 | 2.2 |
| | ≥70 | 1 | 1.4 | 0.8 | 1.8 | 1.9 |
| Kolonel et al., 1988 (*53*) | <70 | 1 | 0.9 | 0.8 | 1.0 | — |
| | ≥70 | 1 | 1.0 | 1.1 | 1.5 | — |
| Mettlin et al., 1989 (*51*) | — | 1 | 1.1 | 0.9 | 1.2 | 1.3 |
| Ohno et al., 1989 (*54*) | — | 1 | 0.8 | — | — | — |
| Ross et al., 1989 (*55*) | | | | | | |
| | Whites | 1 | 1.8 | 1.6 | — | — |
| | Blacks | 1 | 1.4 | 1.9 | — | — |

*As reported in the original studies. Thus, data in this table allow within- but not between-study comparisons.
†Reference category.

## CONCLUSIONS

Although it is difficult to make a precise quantitative assessment of cancer association with high-fat diets in humans, available epidemiological evidence is reasonably consistent for colorectal cancer, for which the relative risk across extreme levels of (saturated) fat intake can be on the order of 2, and a plausible biological framework is available. Epidemiological data are more scanty but also seem to support a positive relationship for ovarian and endometrial cancer, although the evidence of a potential role for dietary fat in the development of breast and prostate cancer is still largely uncertain and controversial, despite a substantial amount of research, particularly for breast cancer.

In addition to the usual indication that more (and better) research is needed, this leaves open to discussion the immediate perspectives for intervention on a preventive and public health scale (*18*, *56*). On the one hand, low-fat diets seem to have a favorable impact on large-bowel cancer and may somewhat reduce the risk of ovarian, colorectal, breast, and prostate neoplasms (as well as of other common cancers, eg, those of the pancreas or gallbladder) and certainly have a favorable impact on cardiovascular diseases. On the other hand, the number of public education strategies against cancer that are feasible in our society is limited, and priorities have to be established. Assessment of priorities requires quantitative evaluation, which is, however, still open to discussion in the field of fats and cancer risk.

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# Cancer Prevention: Optimizing Life-Styles With Special Reference to Nutritional Carcinogenesis[1]

Ernst L. Wynder[2]

**ABSTRACT—Life-style variables, especially those relating to metabolic overload, are significantly linked to risk for human cancer. Although the roles of tobacco use, alcohol abuse, sunlight, and select occupations are well established, the impact of nutrition on human carcinogenesis, and particularly that of excessive intake of fat and low intake of fiber, is less recognized. This article summarizes the essential evidence, recommends optimal fat and fiber intake, and suggests ways in which comprehensive clinical cancer centers can effectively participate in cancer prevention. [J Natl Cancer Inst Monogr 12:87–91, 1992]**

Life-styles, especially those relating to metabolic overload, are important causes of human cancer. Tobacco use, alcohol abuse, exposure to sunlight, unsafe sexual practices, and excessive intake of dietary fat, particularly in view of physical inactivity, all contribute to various prevalent human cancers. Some of the main causative factors have been identified; however, prevention or even intervention is a matter of personal initiative. In most cases, preventive measures require changes, and it is difficult to equate an immediate sacrifice with some possible future gain in wellness.

Key evidence is summarized for the consequences of excessive intake of fat and deficient intake of fiber as they relate to the development of certain cancers. The reports from the National Academy of Sciences and the Surgeon General provide detailed reviews of nutritional carcinogenesis (*1, 2*).

## EVIDENCE

The evidence that tobacco use, alcohol abuse, excessive exposure to sunlight, and sexual promiscuity play roles in human cancer is well known. Although micronutrients and the manner of food preparation are important in nutritional carcinogenesis, these issues are not discussed here. Evidence suggests that specifically fat intake rather than total calories relates to human cancer; only kidney and endometrial cancers are routinely linked to obesity.

Substantial evidence on the linkage of fat intake with various cancers stems from the comparative epidemiology of the United States and Japan (fig. 1). These studies reveal dramatic differences in fat intake over the years (*3*; fig. 2). Table 1 lists the various sources of calories in the United States and Japan over the last 50 years (*4–8*). These differences are not due to genetic makeup, because incidence rates of cancers prevalent in the United States increase in the first generation and more so in the second generation of Japanese migrants to the United States.

Extensive investigations in laboratory rodent models for colon and mammary cancer indicate roles both for fat per se and for the specific type of fat by demonstrating a strong tumor-promoting effect for unsaturated fatty acids and a neutral effect for monounsaturated fatty acids (*9*). Studies also show that fats, especially unsaturated fats, play a role in tumor promotion and tumor progression (*10*). In contrast, fish oils, rich in $\omega$-3 unsaturated fats, generally exert a protective action (*11*).

On the other hand, inhibiting effects have been demonstrated for wheat fiber in both colon and breast cancer models in laboratory animals (*12, 13*). Epidemiological studies in Finland by Reddy et al. (*14*) showed that daily intake of 32 g of fiber/d (the average in rural Finland) increases stool bulk, thereby diluting the bile acid concentration per gram of feces. Colon cancer rates in Finland are low probably because of this factor. Rose et al. (*15*) showed that supplementation with wheat bran fiber reduces the level of estradiols in premenopausal women.

A comparison of cancer rates in southern Italy, northern Italy, and the United States of cancers affected by dietary fat intake, ie, breast, colon, and prostate cancers, shows them to be significantly less common in southern Italy. This is probably due to the lower intake of saturated and polyunsaturated fats in that region, where monounsaturated olive oil is primarily used (*16*). The diverse effect on cancer risk by $\omega$-6 and $\omega$-3 fatty acids is also seen in a study by Rose and Connolly (*17*) showing that human breast cancer cells grow more rapidly in the presence of $\omega$-6 fatty acids and that their growth tends to be inhibited by $\omega$-3 fatty acids.

The best evidence for the hypothesis that nutrition relates to human cancer comes from international studies. National studies, whether retrospective or prospective, are less suitable for documentation of this issue (*18*). The 24-hour dietary recall and the food-frequency questionnaires on which much of the interpretation of food intake by patients and control subjects is based are susceptible to

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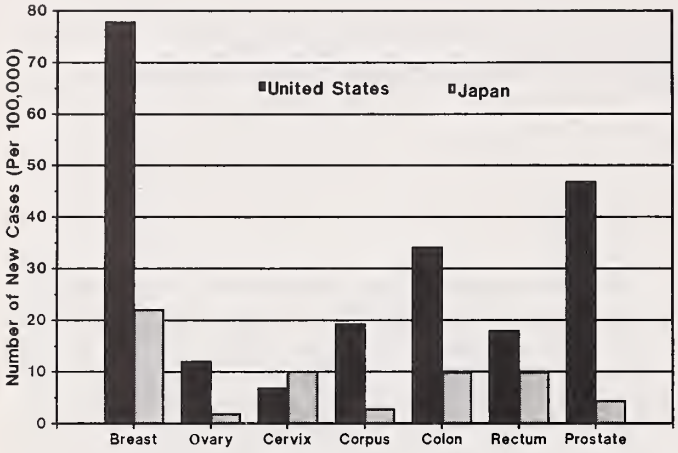


**Figure 1.**—Age-standardized incidence rates for cancer of selected sites in women in United States and Japan, 1980. From International Agency for Research on Cancer: Patterns of cancer in five continents. Lyon: IARC, 1990 (IARC Sci. Publ. 102).

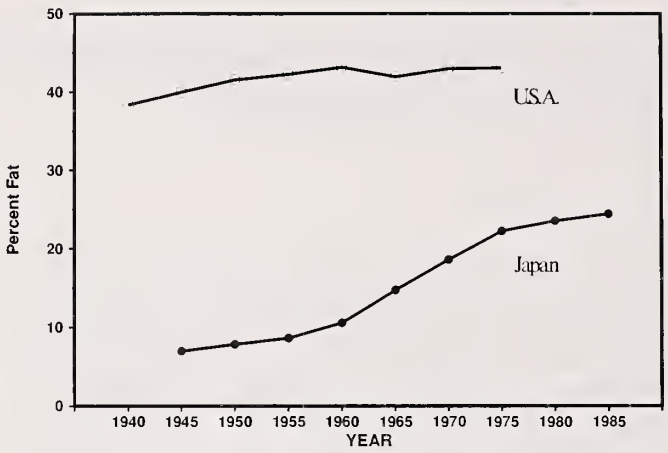


**Figure 2.**—Percentage of total calories attributable to fat in the United States and Japan. Data from US Bureau of Census (1988) and Japan Ministry of Health and Welfare (1986).

errors in measurement and estimation, ie, judgment errors, recall inaccuracies and biases, individual variability, and food-table errors. Such issues are crucial because the range of fat consumption, if measured in a metabolic ward within the general US population, is likely to be found somewhere between 30% and 40% of total caloric intake. Questionnaire information usually indicates only current food intake, which may not have a direct relation ship to food habits 20–30 years earlier, when tumor initiation and early promotion actually began, which was probably a critical period in regard to cancer etiology.

One factor that has been bothersome in retrospective studies is interviewee bias, when a patient may be more likely to underreport fat consumption than a control subject. The existence of such bias should be clear to anyone

**Table 1.**—Net per-capita food supply (g/d), 1934–1985*

| Food | 1934–1938 | 1951–1953 | 1955–1959 | 1960–1964 | 1965–1969 | 1970–1974 | 1975–1979 | 1982 | 1985 |
|---|---|---|---|---|---|---|---|---|---|
| Cereal | | | | | | | | | |
| U.S. | 247 | 207 | 186 | 182 | 178 | 174 | 198 | 161 | 189 |
| Japan | 444 | 430 | 422 | 410 | 380 | 346 | 325 | 305 | 297 |
| Vegetables | | | | | | | | | |
| U.S. | | 312 | 269 | 268 | 270 | 273 | 259 | 260 | 270 |
| Japan | | 190 | 229 | 281 | 322 | 318 | 356 | 358 | 298 |
| Fruits | | | | | | | | | |
| U.S. | | 289 | 210 | 195 | 194 | 196 | 201 | 190 | 191 |
| Japan | | 34 | 48 | 68 | 93 | 113 | 157 | 152 | 102 |
| Red meat | | | | | | | | | |
| U.S. | 195 | 231 | 254 | 268 | 291 | 310 | 314 | 307 | 322 |
| Japan | 11 | 8 | 14 | 26 | 42 | 63 | 84 | 97 | 105 |
| Fats and oils | | | | | | | | | |
| U.S. | 55 | 52 | 57 | 57 | 66 | 66 | 82 | 85 | 91 |
| Japan | 5 | 5 | 9 | 15 | 23 | 30 | 35 | 42 | 40 |
| Eggs | | | | | | | | | |
| U.S. | 44 | 60 | 57 | 51 | 50 | 48 | 44 | 43 | 42 |
| Japan | 8 | 7 | 12 | 24 | 33 | 40 | 44 | 46 | 41 |
| Milk products | | | | | | | | | |
| U.S. | | | 532 | 502 | 490 | 484 | 476† | | |
| Japan | | | 25 | 44 | 67 | 82 | 87† | | |
| Fish | | | | | | | | | |
| U.S. | 14 | 14 | 17 | 17 | 17 | 19 | 20 | 19 | 20 |
| Japan | 49 | 53 | 124 | 101 | 83 | 97 | 102 | 96 | 102 |

*Data are from (*4–8*).
†1975 data only.

**Table 2.**—Variables of meat intake

| |
|---|
| Frequency (day/week/month) |
| Portion size |
| Degree of preparation (rare, medium, well done) |
| Cooking method (eg, charcoal barbecue, broiling, frying, roasting) |
| Type of meat (beef, pork, chicken) |
| Quality of meat (fat content) |
| Removal of fat |

who has interviewed a patient with breast cancer, myocardial infarction, or obesity. Table 2, which lists the various factors influencing fat intake associated with meat consumption, shows that accurate information about the intake of macronutrients or micronutrients in a homogeneous population is virtually impossible to obtain. Hegsted (*19*) stated that "a dietary hypothesis can never be disproved by epidemiological studies within communities," an opinion with which I concur (*20*).

The presentation of Eaton et al. (*21, 22*) comparing Paleolithic and current diets may be helpful in attempting to formulate "optimal dietary intake," (table 3). The high intake of fibers, vegetables, and fruits by prehistoric humans, as determined by analyses of fossilized feces, is especially noteworthy. The intake of saturated fat of these early populations may have been even lower than estimated because whatever meat was eaten was low in fat. Whereas meats currently consumed by humans contain about 20%–30% fat, the meat of wild animals has only 2%–5% fat (*21*). We need to recognize that the fatty meat we eat today is the result of feeding animals corn in feedlots, which is a relatively recent practice. The fat content of these corn-fed cattle is significantly higher than that of grass-fed cattle (*23*; fig. 3). Many chronic diseases of today are a consequence of metabolic overload compared with the Paleolithic period (35 000 years ago).

## BIOMARKERS

Determination of the optimal fat and fiber intake in the diet requires developing biomarkers for certain types of cancer and their associated key risk factors, similar to cholesterol and coronary artery disease. Many studies suggest that, if cholesterol levels for adults are less than 160 mg/dL and for children are about 130 mg/dL, the risk for coronary artery disease would be very low. In this context, we reported an investigation among a group of vegans (*24*). Although their fat intake was about 30% of calories consumed, the average adult cholesterol level was 130 mg/dL; this confirms the significant impact that saturated fatty acids have on hyperlipidemia. Of course, the intake of dietary cholesterol by vegetarians is also exceedingly low. Investigators in the cardiovascular field were unable to find a correlation between dietary fat levels and cholesterol levels in the general US population, which again indicates that dietary assessment involves significant errors in measurement. In regard to a biomarker for breast cancer, Key et al. (*25*) showed that, in rural China, where dietary fat intake is only 15% of calories, the plasma women, who consume 43% of their calories as fat, particularly in the peri- and postmenopausal age groups (45–54 and 55–64 years of age, respectively). In the Women's Intervention Nutrition Study, in which postmenopausal women with stage I and II breast cancer are placed on a diet restricted to 20% fat after standard surgery and in conjunction with chemotherapy or tamoxifen treatment, the reduction of estradiol did not reach the low levels measured in Chinese women (American Health Foundation, unpublished observations). This leads to the question whether the dietary level of fat (20%) is sufficiently low in the diet of the Women's Intervention Nutrition Study.

Fecal bile acid levels were related to colon cancer in various populations. In Japan, the average bile acid concentration was 4.8 mg/g stool; in rural Finland, it was 4.6 mg/g stool, largely due to the increased bulk; and in the United States, it was about 11.7 mg/g stool (*14*, *26*; table 4). Daily stools weighed about 80 g/d in the United States and about 200 g/d in Finland. The optimal amount of stool for a low-risk situation remains to be determined. Biomarkers that can assist in determining "normal" levels as opposed to risks for diseases such as large-bowel and

**Table 3.**—Dietary consumption*

| | Late Paleolithic | Current United States |
|---|---|---|
| Fat, % of calories | 21 | 42 |
| Polyunsaturated-to-saturated fat ratio | 1.4 | 0.44 |
| Fiber, g | 100–500 | 19.7 |
| Sodium, mg | 690 | 2300–6900 |
| Calcium, mg | 1500–2000 | 740 |
| Ascorbic acid, mg | 440 | 90 |

*Data are from (*21*).

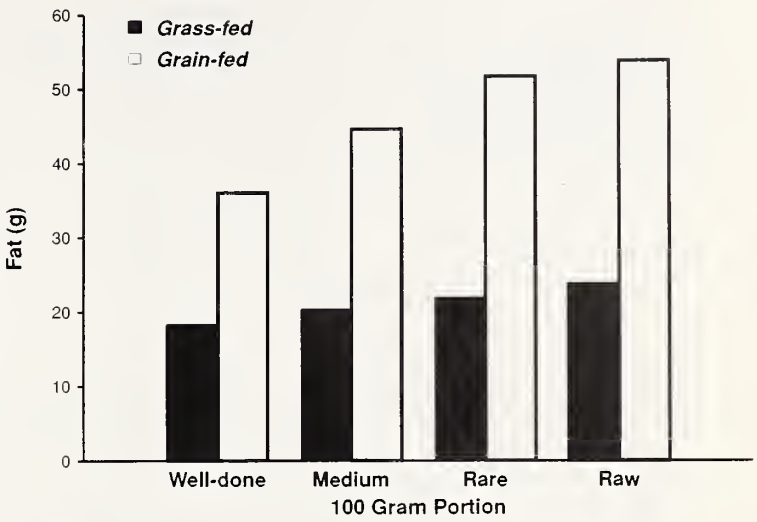


**Figure 3.**—Fat content of beef as affected by type of cooking and method of raising beef cattle. From (*23*).

**Table 4.**—Fecal bile acid excretion and stool output in populations at varied risk for colon cancer*

| Population | Bile acid excretion, $mg/g^{-1}/d^{-1}$/stool | Daily stool output (on dry-matter basis), g/d | Fiber intake, g/d | Fat intake† |
|---|---|---|---|---|
| Metropolitan New York | 11.7 | 22 | 12–14 | + + + |
| Rural Kuopio, Finland | 4.6 | 60 | 28–32 | + + + |
| Urban Helsinki, Finland | 7.4 | 50 | 21–23 | + + + |
| Japan | 4.8 | 23 | 10–12 | + |

*Data are from (*14*, *26*).
†The following score has been assigned based on available nutritional data: + + +, high intake; + +, moderate intake; +, low intake.

estradiol levels are significantly lower than among British hormone-dependent cancers must be investigated. This would allow more judicious evaluation of the optimal diet than food records.

Although a full understanding of the interaction between tumorigenic agents and the host is not required to make public health recommendations, mechanistic studies should be pursued to develop some leads for preventive strategies. Among the mechanisms whereby dietary fat can affect carcinogenesis, its effects on the endocrine, autoimmune, and immune systems; oncogene activation; gut bacteria; membrane structure; and lipid perioxidations must be considered. Examination of the variables reveals that fat not only contributes to calories but also influences the pathways by which various cancers develop.

## PUBLIC HEALTH RECOMMENDATIONS

On the basis of observed correlations, the American Health Foundation recommends a food plan that is lower in fat than the current plan suggests. Such an "optimal" food plan may not be ideal, but it can be accomplished within traditional and economic settings. I propose that total fat intake should be about 25% of total calories. At this level, the type of fat may not be as important as it appears to be at a higher level of intake. The fiber intake should be about 25 g/d, with an equal distribution between soluble and insoluble fibers. For health promotion, this can be called a 25:25 diet. Establishing this dietary regimen for the nation will require better education, better food labeling, and greater cooperation by the food industry to produce foods with higher fiber and lower fat content. Progress is already being made by the dairy and meat industries in this regard. In addition, the food industry has the capacity to appropriately inform consumers through educational advertising.

Nutritional habits, in addition to other life-style variables, are initiated early in life. Therefore, the American Health Foundation (*27*) has focused on comprehensive health education starting at an early age. The American Health Foundation's Know Your Body program includes workbooks for students; guides for teachers; an annual evaluation for knowledge, attitude, and behavior; yearly health screening; and a full-time health educator who organizes all health-related activities. The coordinator is also responsible for getting parents involved. Nutrition can be regarded as an effective entry for modification of other health behaviors such as use of tobacco and illegal drugs and alcohol abuse. Thus, nutrition counseling should be emphasized as an initiator and indicator of good health behavior. In addition, children receiving such counseling may act as agents of behavioral change for their families. Nutrition educators should therefore regard themselves as activists in the increasingly important field of youth health education.

In summary, the optimal fat and fiber intake is clear. How best to achieve these levels for the entire population remains to be determined.

In respect to cancer prevention, to what extent can comprehensive clinical cancer centers play a role? Cancer prevention units should be established within such centers (table 5). Units serving both the patient population at the center and the community at large could provide education for optimal nutrition and other issues related to cancer prevention and early detection. Local media should also be involved. Together, these vehicles bring the opportunities of cancer prevention to the attention of all segments of society.

**Table 5.**—Ideal disease prevention control centers

| |
|---|
| Staff |
| Physician |
| Epidemiologist |
| Behavioral scientist |
| Behavioral change interventionist |
| Public health nurse |
| Nutritionist |
| Adolescent health promoter |
| Geriatric health promoter |
| Mass media and marketing specialist |
| Target |
| Community |
| Individual |
| Family |
| School |
| Work site |
| Church |
| Medical care facility |

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# Chemoprevention of Breast Cancer With Retinoids

Umberto Veronesi, Giuseppe De Palo, Alberto Costa, Franca Formelli, Ettore Marubini, *and* Marcella Del Vecchio[1,2]

**ABSTRACT—Fenretinide [*N*-(4-hydroxyphenyl)retinamide, 4-HPR] is an effective agent for the inhibition of *N*-nitroso-*N*-methylurea-induced breast cancer in rats. This compound has been studied extensively and proved to be safer and less teratogenic than many other retinoids. A major characteristic of 4-HPR is its ability to concentrate in the granular and fat tissue of the breast instead of in the liver. Between January and June 1986, we carried out a phase I study on 101 patients divided into four randomized groups receiving placebo and 100, 200, and 300 mg/day of 4-HPR. Patients received the drug for 6 months without any major toxic effect. This finding was confirmed by another 6-month study in which patients received a common dose of 200 mg/day. In March 1987, a phase III study was started to evaluate the effectiveness of 4-HPR in preventing contralateral primary tumors in women who had already been treated for breast cancer. If 4-HPR succeeds in preventing second primaries in breast cancer patients, it may be useful for a wider group of subjects at high risk for breast cancer. This randomized study was designed with two arms: an intervention group versus a group receiving no treatment. Patients in the intervention group will be treated with 200 mg/day 4-HPR for 5 years. Patients in the control group will not be treated. A further 2 years of follow-up is planned for both groups. Currently, 2450 patients have been recruited. We expect a total accrual of 3500 patients by the end of 1992. [J Natl Cancer Inst Monogr 12:93–97, 1992]**

The incidence of breast cancer is rising continuously in most world populations (*1*). Although improved detection and treatment procedures are likely to increase the survival rate of breast cancer patients, research programs directed at reducing its incidence are absolutely necessary. Among the many existing prevention hypotheses, "chemoprevention" appears promising.

The original proposed definition of chemoprevention refers to the prevention of cancer with pharmacological agents to inhibit or reverse the process of carcinogenesis (*2*). Chemoprevention therefore focuses on the biology of tumor promotion and progression and on the mechanisms by which the tissue dedifferentiation caused by spontaneous mutation, carcinogens, or promoting agents can be overcome (*3*). Chemopreventive agents can be classified according to mechanisms of action into three main categories: 1) compounds effective against complete carcinogens, 2) compounds effective against tumor promoters, and 3) compounds competing at the cell-receptor level with proliferation-stimulating agents. The first category consists of compounds that prevent the development of carcinogens from precursor substances (eg, tocopherols), compounds that prevent carcinogens from reaching or reacting with critical target sites (eg, phenothiazines), and compounds that suppress the formation of neoplasia in cells previously exposed to a carcinogenic agent (ie, retinoids). The second category is composed of antioxidant compounds that protect the tissue from attack by oxygen radicals (eg, dexamethasone). Tamoxifen, an antiestrogen, represents the third category, and acts by blocking the activity of estradiol in the tissue by competing for receptors.

Retinoids include all natural and synthetic analogues of vitamin A. These agents prevent neoplastic formations in cells previously exposed to carcinogens by inducing and enhancing cellular differentiation. The chemopreventive properties of retinoids have been demonstrated by in vitro and in vivo studies. In vitro studies on human tumor cell cultures indicate that retinoids exert significant activity against lung, breast, and ovarian cancers and melanomas (*4*). In vivo studies in experimental animals have suggested that retinoids may be effective inhibitors of chemical carcinogenesis in skin, breast, esophageal, respiratory tract, pancreatic, urinary bladder, and colon cancers (*5*).

The principal factor limiting the clinical use of retinoids is toxicity, because they tend to create hepatic damage by accumulating in the liver. In 1979, a synthetic retinoid, fenretinide [*N*-(4-hydroxyphenyl)retinamide, 4-HPR], was described by Moon et al. (*6*) as an effective agent for the inhibition of *N*-nitroso-*N*-methylurea-induced breast cancer in rats. This compound has since been studied extensively and proved to be safer (*7*) and less teratogenic (*8*) than many other retinoids. A major characteristic of 4-HPR is its ability to concentrate in the granular and fat tissue of the breast instead of in the liver (*6*). Its inhibition of carcinogenesis is enhanced by oophorectomy in rats with *N*-nitroso-*N*-methylurea-induced mammary cancers. This suggests that 4-HPR may be highly effective in inhibiting ovarian hormone-independent tumors and that its activity is not mediated via ovarian hormone action. Further studies have demonstrated that circulating levels of estradiol, testosterone, dehydroepiandrosterone sulfate, prolactin, luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin are not modified or influenced by 4-HPR treatment in women (*9*). Finally, 4-HPR can enhance the anticarcinogenic action of

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tamoxifen (*10, 11*); animal studies suggest a more efficient action of combined 4-HPR and tamoxifen administration compared with that of either agent alone in preventing, after removal of the primary mammary tumor, the development of subsequent tumors (*12*).

## TRIAL HISTORY

The interest of the Milan National Cancer Institute in the study of chemoprevention with retinoids dates to 1978, when a special subcommittee was appointed to study the possibility of identifying a group of women in the general population who would be good candidates for a chemoprevention trial with retinoids. After 2 years, the committee could not recommend any segment of the population for the study. It appeared difficult to recruit the cases at highest risk of breast cancer among the general population; in addition, there are few true high-risk factors. Therefore, one of us (U.V.) suggested studying patients who had already been treated for breast cancer. The concept was that a patient who has been treated for a small early tumor has a good prognosis (~80%–90% survival) but has a high risk of developing contralateral breast cancer. The first advantage of this model is that the incidence of contralateral breast cancer is high in patients who have experienced a primary breast tumor (~0.8%/year). Second, for patients already under medical surveillance with periodic follow-up, it is easier for them to participate in a long-term study. Third, compliance in this group of patients is expected to be much higher than in the general population.

In 1983, the first randomized research protocol was developed for about 3000 patients who already had been treated for breast cancer and had a good prognosis for survival. It took about 3 years to decide on the final test protocol (*13*).

Between January and June 1986, we carried out a phase I study on 101 patients divided into four randomized groups receiving placebo and 100, 200, and 300 mg/day of 4-HPR. These patients received the drug for 6 months without any major toxic effect. This finding was confirmed by another 6-month study with a common dose of 200 mg/day. The protocol for a phase III randomized study was finally approved by our ethical committee, after which it took about 6 months to develop the technical setting of the study, train the personnel, and recruit additional doctors. In March 1987, we began the phase III study, and 2450 patients have so far been recruited. A total accrual of 3500 patients is expected by the end of 1992.

## STUDY DESIGN

This randomized study is expected to evaluate the effectiveness of 4-HPR in preventing contralateral primary tumors in women who have already been treated for breast cancer. If 4-HPR succeeds in preventing second primaries in breast cancer patients, it may be useful for a wider group of subjects at high risk for breast cancer. This completely randomized study was planned with two arms: an intervention group versus a group receiving no treatment. Patients in the intervention group will be treated with 200 mg/day 4-HPR for 5 years. Patients in the control group will not be treated (fig. 1). A further 2 years of follow-up are planned for both groups. Treated and untreated patients will receive the same clinical and laboratory follow-up.

### Eligibility

Study participants are breast cancer patients between 35 and 65 years of age. To qualify for the study, patients must have had an operated breast cancer (T1-2) without axillary lymph node involvement and without evidence of local recurrence and/or distant metastases. Patients must have normal metabolic, liver, and renal function tests in addition to normal lymphocyte, erythrocyte, and platelet counts. Due to the teratogenic effect of 4-HPR, patients must be willing to use contraception during the study and for 6 months after the end of intervention. Patients are not allowed to start any intense diets during intervention; this is to avoid any severe decrease in the body fat where 4-HPR will presumably be stored, which could result in a dangerous increase of 4-HPR serum levels. Patients are informed of the benefits and risks of the study and are asked to participate for the entire duration of the study. In addition to the general criteria for exclusion, which apply to all clinical trials, the following criteria for ineligibility will also be considered: postsurgical chemotherapy or endocrine treatment, concurrent use of high-dose vitamin A (>30 000 IU/day), hypovitaminosis A, documented hypersensitivity to retinoids, and tapetoretinal degeneration (or a family history thereof).

### Diagnosis, Staging, and Treatment of Breast Cancer

The diagnosis is controlled with the patient's clinical record. The histopathological diagnosis must be per-

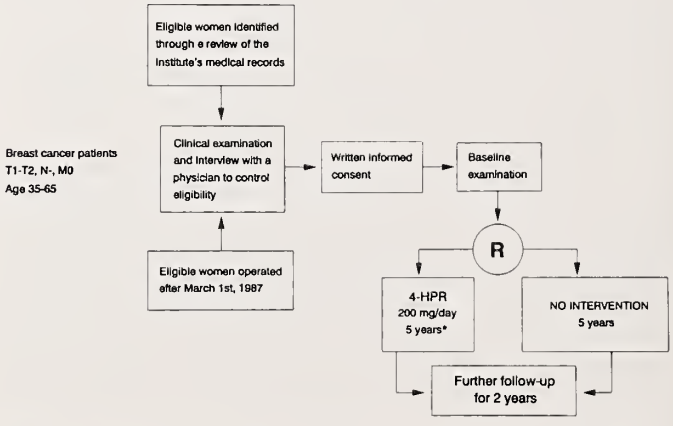


**Figure 1.**—Study design and intervention plans.* It is recommended that 4-HPR be taken after evening meal, and a 3-day break from 4-HPR is prescribed for all patients at end of each month to increase serum retinol levels.

formed or reviewed by an institute pathologist. The histological categories considered are invasive and intraductal carcinomas. The stage of the neoplasm is controlled, verifying the maximum diameter of the neoplasm according to the histopathological report. There must be no axillary node involvement. The status of metastases will be controlled by a chest x ray, bone scan, blood tests for liver function, and liver ultrasonography. The estrogen receptor status is determined in all patients.

The type of primary tumor treatment is specified, ie, conservative treatment such as quadrantectomy or tumorectomy plus axillary dissection and radiotherapy or ablative treatment such as Halsted, Patey, or Madden mastectomy with or without radiotherapy. Because the possibility of an unfavorable event is linked to the duration of time after surgery, the date of surgery is accurately recorded, and this parameter will be taken into account in the statistical analysis. Conservative surgery includes tangential radiotherapy on the residual breast. The possible carcinogenic effects of radiation will be considered in the statistical analysis even if the absorption of radiation by the contralateral breast seems to be very low with the routine technique.

### Ophthalmologic Questionnaire

Particular attention is devoted to night vision, and dark adaptation will be checked in all eligible subjects by an ophthalmologic questionnaire reported in table 1. The ophthalmologic questionnaire will be considered positive if at least two of three items are positive, doubtful if one of three items is positive, and negative if none of the items is positive. All subjects with a positive ophthalmologic questionnaire will be asked to undergo a visual field test and an electroretinogram (ERG). The ERG examination will be performed on an Amplaid MK7 electrodiagnostic computer system. The parameters will be those proposed for the Amplaid MK7 ERG recording. If the visual field test and the ERG are normal, the subject will be considered eligible.

**Table 1.**—Ophthalmologic questionnaire

*Check the appropriate response*

*At baseline*

1. Dark adaptation:
   In comparison with other people around you, do you adapt easily from light to semiobscurity, when going into a cinema and the film has already started?
   ☐ Yes ☐ No ☐ Not applicable
2. Vision in condition of poor luminosity:
   In a domestic and semiobscure environment, are you able to perceive the outlines of objects?
   ☐ Yes ☐ No ☐ Not applicable
3. Recovery after dazzling:
   When you pass from a semiobscure environment to a strongly lit one, do you remain dazzled?
   ☐ Yes ☐ No ☐ Not applicable

*During follow-up: Modification since the start of treatment*

1. Dark adaptation:
   ☐ No ☐ Improved ☐ Heightened
2. Vision in condition of poor luminosity:
   ☐ No ☐ Improved ☐ Heightened
3. Recovery after dazzling:
   ☐ No ☐ Improved ☐ Heightened

### Determination of Plasma Retinol Levels

Because it has been shown that 4-HPR administration lowers plasma retinol concentration (*14, 15*), retinol levels will be assessed at baseline.

## RANDOMIZATION

Patients may enter the study through one of two mechanisms: 1) those identified as potentially eligible through a review of breast cancer medical records and 2) those who will be operated on during the period of patient enlistment and prove to be eligible.

The following clinical variables will be taken into account in the statistical analysis: menopausal status, time of duration after surgery, radiotherapy after surgery, and body weight. Eligible patients are randomly divided into the intervention or control groups. Patients identified as eligible for the study through one of the two methods described will be invited to an interview with a physician involved in the study. By this time, the patients identified through a review of the institute's medical records will have already received a letter announcing the study and explaining its aim. If the patient is willing to participate in the trial and if she is eligible according to the criteria listed above, she is visited and invited to read and sign an informed consent form. Her clinical record will be started, the baseline form will be filled out, and appointments will be made for performing all the baseline examinations.

## FOLLOW-UP

The aims of the follow-up are to evaluate the efficacy of the drug, monitor the disease, and obtain information on the mechanism of action of 4-HPR. The tests to be performed are all summarized in table 2. Mammography will be repeated every year mainly to monitor the contralateral mammary gland. A sample of mammograms will be blindly reviewed by a senior radiologist. Needle biopsies will be performed on all lumps considered suspicious either by clinical examination and/or mammography. Cytological examination will be blindly performed by a senior pathologist. Excisional biopsy will be planned for all lumps considered suspicious by both clinical examination and mammography. Chest x rays will be performed every year and bone scans every 18 months to monitor lung and bone metastases. The plasma concentrations of 4-HPR, 4-MPR (a metabolite of 4-HPR), and retinol will be assessed during the entire intervention period to evaluate

Table 2.—Follow-up during the first 5 years

| Tests | Months | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 6th | 12th | 18th | 24th | 30th | 36th | 42nd | 48th | 54th | 60th |
| Physical examination | X | X | X | X | X | X | X | X | X | X | X |
| Mammography | X | | X | | X | | X | | X | | X |
| Chest x rays | X | | X | | X | | X | | X | | X |
| Bone scan | X | | | X | | | X | | | | X |
| Liver ultrasonography | X | | X | | X | | X | | X | | X |
| Laboratory determinations* | X | X | X | X | X | X | X | X | X | X | X |
| Retinol blood levels† | X | | X | | X | | X | | X | | X |
| 4-HPR, 4-MPR blood levels† | | | X | | X | | X | | X | | X |
| Pregnancy test | X | | | | | | | | | | |

*Hemoglobin, hematocrit, leukocytes, erythrocytes, platelets, SGOT, SGPT, total bilirubin, alkaline phosphatase, blood glucose, cholesterol, triglycerides, creatinine, blood urea nitrogen.

†In all treated subjects.

compliance and to determine whether these levels are related to 4-HPR toxicity and/or activity. Plasma concentrations will be determined on a yearly basis because patients taking 200 mg/day 4-HPR for 1 year have had 4-HPR and retinol levels similar to those found at 5 months, suggesting no drug accumulation and no further retinol reduction (*15*).

## EFFICACY MEASUREMENTS

The main measurements of efficacy will be physical examination and mammography of the contralateral breast. Mammography will be taken first at baseline and then yearly to detect contralateral tumors; a senior radiologist will blindly review a random sample of mammograms without being informed of the patient's name and without knowing whether the x rays belong to a treated or untreated patient. Low-dose mammography will be performed. Special additional mammograms will be performed on premenopausal patients who have radiopaque breasts that are difficult to evaluate. Chest x rays and bone scans will be periodically performed together with laboratory blood determinations to evaluate the clinical situations of the patients and the side effects they experience with regard to the first primary tumor.

The appearance of contralateral breast cancer, local ipsilateral recurrence, distant metastasis, or second primary tumors in other organs will be considered unfavorable events. Unfavorable events will be considered at the time they are clinically and/or radiologically documented.

The intervention will last 5 years for each patient. Although the chemopreventive action of retinoids probably ends when administration of the drug is stopped, the follow-up period, after the intervention, should be as long as possible—at least 2 years. Patients who have metastases or local tumor recurrences will be treated accordingly and will be followed in the current trial for survival evaluation.

## STATISTICAL CONSIDERATIONS

The major end point of this study is the appearance of contralateral breast cancer. The incidence of contralateral cancer is defined as the occurrence of the first new cancer in the opposite breast at any time during the observation period (intervention plus follow-up). The major analysis will compare the curves for the cumulative incidence of new contralateral primaries over time; the log-rank two-sample test will be used to perform this comparison.

Baseline characteristics (prognostic factors) will be investigated to assess possible imbalances between the two groups and will include all the factors that are prognostic for breast tumors (eg, age, menopausal status). Cox's proportional hazard regression model (*16*) will be adapted to allow comparison between the above factors and the responses observed in the two arms of the trial. The aim of this approach is twofold: to adjust for possible imbalances and to increase the precision of the estimation of the treatment effect. The time elapsing from surgery to recruitment into the study will also be inserted into the model because it is thought to be a prognostically relevant variable.

Comparison of the two treatment groups in terms of frequency of patients developing adverse reactions will be performed by logistic regression analysis. This analysis will be adapted to also cover severity levels and duration of adverse events. Although the main emphasis will be on comparing all patients randomized into the two groups, some explanatory comparisons will be made among patients who complied well with the intervention and those who did not.

Due to the length of the follow-up of this trial (7 years), it has been considered questionable to rely on the "fixed-sample-size" approach, ie, to make any inference about treatment effects until the information on all patients has been gathered. Therefore, interim analyses will be performed at the 2nd, 4th, and 6th years from the beginning of the trial; the "group-sequential" log-rank tests will be assessed by using the conservative boundaries suggested by O'Brien and Fleming (*17*).

### Sample Size

The required sample size for this trial has been computed according to Wu et al. (*18*). Contralateral cancer in breast cancer patients has an estimated incidence rate of 0.8%/year. This implies that the probability of not developing the disease in a 7-year period is $P = \exp(-.056) = .94554$.

Clinical considerations support the hypothesis that the possible efficacy of 4-HPR to halve the risk of contralateral breast cancer will be shown after only 3 years of intervention. As a matter of fact, there is no evidence that 4-HPR has any antitumor activity; we do not expect, then, that it can have any effect on microscopic contralateral cancers already present at the time of randomization that are undetectable by both clinical examination and mammography. Therefore, by assuming that a 3-year lag is needed to obtain full intervention efficacy, by ensuring that all patients are followed for at least 2 years after the end of intervention, and by using the approach of Wu et al. (*18*), the required sample size is 3500. This figure is obtained by adopting a two-tailed test with $P = .05$ and $1 - B = .90$ for the expected relative 50% reduction in the incidence rate of contralateral cancer.

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# Potential Impact of Sugar and Fat Substitutes in American Diet

John P. Foreyt *and* G. Ken Goodrick[1]

**ABSTRACT—Nonnutritive sweeteners and fat substitutes have achieved rapid consumer acceptance. This is largely due to the perception held by the public that these products are helpful in weight control and diet improvement. The cognitive component in human eating behavior makes it difficult to generalize from animal research. The effectiveness of these products in weight control has yet to be demonstrated conclusively in human research. Currently these products appear to add palatibility to reduced-calorie diets and may be helpful to weight-loss efforts as part of an overall balanced, nutritious diet and healthy life-style that includes exercise. [J Natl Cancer Inst Monogr 12:99–103, 1992]**

On average, an American consumes 14 tablespoons of sugar and 12 tablespoons of fat each day. The addition of refined sugar to the diet is popularly thought to be one reason for excess calorie consumption and obesity. Reduction of calorie intake and of obesity may reduce the risk for some types of cancer, including cancers of the breast, colon, and prostate (*1–5*). Dietary fat has also been implicated in cancer risk (*4, 6, 7*). The National Cancer Institute (*8*) and the American Cancer Society (*9*) have recommended avoidance of obesity and reduction of total fat intake to 30% or less of calories. Whereas investigations on the impact of dietary fat and obesity on cancer risk continue to find increasingly supportive evidence, we examine the potential use of sugar and fat substitutes as aids in the clinical or self-applied efforts to reduce obesity and dietary fat.

## NONNUTRITIVE SWEETENERS

The predilection for sweet taste appears to be inborn in humans (*10*). Such an affinity may be adaptive in directing appetite toward healthful fruits and away from dangerous bitter substances. Archeological findings reveal gathering of honey at least 20 000 years ago (*11*), and until about 200 years ago, most sweetness came from honey or fruits. In the late 1700s, sugarcane and sugar beets were recognized as rich sources of sugar, and it was well into the next century before processing methods allowed for mass distribution of refined sugar.

By the middle of the twentieth century, refined sugar was being added to many foods, causing many people to be alarmed about the "empty" calories provided by sugar, the potential of sugar to cause overeating and obesity, and the increased risk of dental caries. The increasing prevalence of obesity with the advent of a more sedentary culture, together with the association of sugar with high-calorie-density foods such as desserts, may have helped make sugar appear to be the villain in the fight against obesity. Despite a lack of evidence that sugar poses a health hazard other than for dental caries (*12*), nonnutritive sweeteners (NNS) became favored by "dieters" and have become accepted by most Americans regardless of weight status.

The discovery of saccharin over 100 years ago allowed sweetness without appreciable calories, in that it is about 300 times sweeter than sucrose. Aspartame, about 180 times sweeter than sucrose, has become popular and is now used in more than 1500 food products. Acesulfame, developed by Hoechst, has been approved by the US Food and Drug Administration and is about 200 times sweeter than sucrose. Other recently developed sweeteners include Sucralose (McNeil), Alitame (Pfizer), and Sweetener 2000 (Monsanto). They are 600, 2000, and 10 000 times sweeter than sucrose, respectively.

Use of saccharin has gradually increased. In 1984, the amount of saccharin used was equivalent to about 1.1 million tons of sugar. Aspartame was introduced in 1981. From 1981 to 1984, aspartame use rose to the equivalent of 400 000 tons of sugar. During the same 3-year period, sucrose consumption fell about 1.15 million tons to about 8 million tons (*13*). The sweetness market share of NNS appears to be growing rapidly, especially for aspartame.

Soft drinks sweetened with aspartame have become amazingly popular; about half of a typical supermarket soft-drink aisle contains sugar-free drinks. During the growth in sugar-free drink sales, sugar-containing soft-drink sales have not declined. This suggests that Americans are increasingly substituting sugar-free drinks for water (*14*), either for prevention of obesity or for the enjoyment of sweet taste. Marketing strategies sometimes attempt to associate sugar-free drinks with slimness and fitness, even though nutritionally only water is involved.

## NONNUTRITIVE SWEETENERS AND WEIGHT CONTROL

Although the general public believes that NNS are helpful in weight control, there has been controversy among researchers. Animal research has yielded conflicting results, possibly due to the complexity of appetitive mecha-

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nisms. For example, Tordoff (*15*) points out that rats given a saccharin solution eat 15% more food than when given only water. The theory is that sweet taste increases food intake by producing biochemical changes in the liver that increase fuel storage and consequently decrease fuel oxidation. However, long-term overeating due to saccharin ingestion may be counterregulated by an increased level of fat fuels available for oxidation, which may explain why rats given continuous access to saccharin do not become obese (*15*). However, when saccharin is added to an oil-water emulsion, rats show an increased intake of 50% that persists and produces rapid weight gain (*16*). The fact that many human foods that pose a problem in weight control are sweet with high fat content might lead individuals to avoid NNS in the context of meals to minimize the risk of overeating.

In a study of the effects of NNS on body weight in rats, one group of rats was given a sucrose solution, and another group received an aspartame and saccharin solution (*17*). The sugar-fed rats gained weight, whereas the NNS-fed rats showed the same weight gain as control water-fed rats. When the sugar solution was replaced with the artificially sweetened water, the rats that had gained weight now lost. This argues for the potential efficacy of artificial sweeteners in producing weight loss in obese humans that have been on a diet containing sugar.

The above discussion is not intended to be an exhaustive review of animal studies on the effects of nutritive and nonnutritive sweeteners on eating behavior. It does demonstrate that the mechanisms that control eating in animals are so complex that seemingly contradictory results can be obtained depending on the manipulation of many variables. The effect of sweets on eating appears to be modulated by the level of protein and fat in the diet, whether the sweetener is presented in dry or wet form, the sex of the animal, and whether the animal has been reared free of virus and antibodies (*18*).

This complexity makes generalization to humans difficult. Moreover, human eating seems to be controlled largely by cognitive factors, especially among those with a history of trying to lose weight. The perceived social pressure to be thin drives many to extremes. In our clinical experience, there have been patients who can drink a sugar-free soda and be satisfied; others find that any consumption of sweets, nutritive or nonnutritive, sets them off on week-long binges.

To discover the potential impact of NNS on weight control, it is necessary to look at the short- and long-term effects on eating and body weight. In the short term, does use of NNS cause excessive eating? The hunger and food intake of normal-weight young men does not seem to be affected by drinking aspartame-sweetened soft drinks (*19*). When normal-weight nondieting subjects are given pudding or gelatin sweetened with sugar or aspartame, they eat about the same amount at the next meal, with no differences in hunger, fullness, or measures of satiety (*20*). This effect was found even when subjects were told of the calorie content of the foods. The researchers point out that knowledge of the energy content of foods may affect later intake only in those who consciously try to restrain their eating due to weight problems. Again, the generalizability of such studies can be questioned due to differences in cognitive mechanisms between normal-weight and overweight subjects.

To help elucidate differences between overweight and normal-weight individuals' gustatory responses to different sweeteners, Rodin (*21*) gave subjects 0.5 L of water sweetened with fructose, glucose, or aspartame. She found that an aspartame-sweetened drink did not lead to greater subsequent food intake than did a preload of plain water. Rodin also assessed plasma insulin levels periodically after the preload drink. Some have speculated that the sugar → hyperinsulinemia → hypoglycemia → hunger → increased eating cycle could be conditioned to the taste of NNS and that, for this reason, artificial sweeteners should be avoided to control eating. However, Rodin found that aspartame produced no changes in plasma insulin.

Rodin's finding that the fructose preload produced the lowest overall calorie consumption and the least fat intake during the subsequent ad libitum buffet is important to overweight individuals. If this effect is shown to continue in long-term studies, then obese people should probably switch to fructose, at least for their premeal beverages.

If long-term use of NNS were helpful in weight control, a significant relationship between use and weight might show up in surveys of free-living individuals. In a study of 78 694 women aged 50–69 years, it was found that higher usage of NNS was associated with higher body mass index (*22*). Users gained more weight than nonusers over a 1-year period, but the difference in weight gain was not clinically significant, ranging from 0.5 to 1.5 lb more. These data suggest that use of NNS is not the answer to weight control. However, users might have gained even more weight if they had not had access to NNS. Also, the study relied on self-reported body weights and sweetener use and excluded subjects who had changed their dietary habits over the previous 10 years.

More pertinent to the determination of the efficacy of NNS in weight control are studies in which use of NNS is experimentally compared with use of sugar in the diet over time. Monkeys given sucrose solutions to drink compensated accurately by reducing their food intake so that calorie intake remained constant; when given aspartame-sweetened fluids, the monkeys briefly ate less but then resumed normal eating (*23, 24*). Thus, for monkeys at least, NNS does not fool energy regulatory systems. Such a response would have no effect on weight.

Humans are reared on a sugar-sweetened diet and continue to enjoy sweetness from sugar or NNS. Thus, the substitution of NNS for sugar may produce an effect different from that found in monkeys. When foods normally sweetened with sugar were replaced with aspartame-sweetened items, obese and nonobese subjects showed a sustained 15% decrease in total energy intake (*14*). However, these results must be compared to those of control groups in which no substitution for sugar is made under the same feeding conditions to conclude that substitution

of NNS has a beneficial effect that would generalize to free-living humans (*14*).

To discover whether aspartame-sweetened sodas aid in the control of long-term food intake, Tordoff and Alleva (*25*) gave free-living normal-weight subjects 1150 g of soda sweetened with aspartame or high-fructose corn syrup in a counterbalanced design of 3 weeks each of aspartame, syrup, or no experimental beverages. The aspartame condition significantly reduced total calorie intake by 179 kcal/d (7% decrease), whereas the syrup condition reduced intake by 195 kcal/d (13% increase), failing to compensate fully for the 530 kcal in the drinks.

These studies suggest that, when sugar is covertly replaced by aspartame, significant reduction in overall calorie intake occurs. However, under normal circumstances, humans will know whether they are using NNS or sugar. This may affect their hunger through cognitive mechanisms and may lead dieters to eat more, knowing that they have reduced their intake by using NNS.

In a more traditional study of the effect of aspartame in weight loss, Kanders et al. (*26*) compared behavioral treatment of obesity with and without aspartame. The control group went on a balanced deficit diet and was prescribed an exercise program. The experimental group was instructed to add two or more aspartame-sweetened low-calorie foods daily while maintaining the same calorie level. Both groups lost about the same amount of weight. Because of the difficulty in separating out an individual effect of one treatment component, it can only be concluded that there is no disadvantage to using aspartame within the context of such a treatment program. Interestingly, these researchers monitored reported carbohydrate cravings throughout their study. Cravings increased equally for both groups, indicating that the calorie deficit, rather than any special quality of the foods eaten or the aspartame, was probably responsible for the level of craving.

On the basis of this brief review, the use of NNS does not seem counterproductive to weight-loss efforts. Rolls (*27*), in a review of NNS on appetite and food consumption, concludes that NNS have never been found to cause weight gain in humans. Booth (*28*) cites studies indicating that reduction of sugar in the diet will not be effective in helping weight reduction. He feels the emphasis on artificial replacement of calories should focus on fat replacement. Future research should investigate whether there is a danger that use of aspartame to avoid calories during dieting may make it pyschologically easier to arrive at the level of energy deficit at which physiological counterregulatory mechanisms take over eating control, resulting in binge eating (*29, 30*). On the positive side, use of NNS allows for a greater variety of sweet foods within a given calorie-deficit diet.

## FAT SUBSTITUTES

Among animals in natural settings, reproduction, territoriality, and eating behavior interact in such a way that energy sources are limited. It is adaptive to have a large appetite for energy-dense foods to capitalize on the opportunities to obtain energy. Humans seem to have a predilection for fats, possibly due to such evolutionary adaptive mechanisms. Apart from this, humans like to eat fat for the texture, including the smoothness or creaminess of ice cream or the crispiness of frying. There may also be physiological and learning mechanisms that account for higher-than-desirable fat consumption (*31*).

The US diet currently contains about 36% of energy as fat. The recommended level is 30% (*4*). Excessive fat intake may be a risk for certain kinds of cancer (*6*) and obesity (*32*). Attempts to lower the fat content of the US diet are generally not successful, due to the reduced palatability of the more healthful diet (*33*).

The only way to maintain palatability and reduce fat is to use fat substitutes. Food technologists have been able to produce acceptable fat substitutes from modified starches and gums. Such products include polydextrose (a starch polymer), maltodextrin (made from hydrolyzed cornstarch), and tapioca dextrin. These are used to make the new fat-free bakery goods, as well as puddings, frostings, and salad dressings. They vary in calorie density from 1 to 4 kcal/g.

A newer development is the advent of fat replacements, chiefly olestra and microparticulated proteins (MPP). Olestra is synthetic sucrose polyesters; the molecules are too large to be digested, and thus, olestra provides no calories. MPP are made by processing whey or egg albumin into such tiny spheres that they resemble globules of emulsified dairy fat, so that the texture is smooth and creamy. MPP have a calorie density of only 1–2 kcal/g.

## IMPACT OF FAT SUBSTITUTES

These fat replacements are so new that independent research results on usage and efficacy in diet-modification programs are not yet available. It is projected that olestra might reduce the dietary fat content by 2% (*33*). Full usage of MPP in foods could potentially reduce the fat content from 36% to 32% (*34*). These reductions could have a modest impact on the level of obesity (*32*). It remains to be seen whether fat replacements will be able to satisfy psychological needs for fat and whether a diet reduced in fat via replacements will stimulate any digestive/appetite mechanisms that result in undue cravings. These factors may impact the ease with which humans can maintain prudent eating with the use of fat replacements.

Speculation about the long-term impact of fat substitutes in the US diet includes several concerns. The use of MPP may increase the protein intake in the US diet, which is already too high and may pose a risk for kidney disease. However, the amount of increase may be too slight to have such an effect (*34*). If olestra is made more palatable by being made less viscous, anal leakage may occur (*35*). The disposal of undigestible olestra into the sewer systems may pose a problem for normal biological sanitation methods (*35*).

## SUMMARY AND RECOMMENDATIONS

The arrival of fat substitutes and NNS has been a boon to weight-conscious Americans. Whereas the effectiveness of these products in weight control has yet to be demonstrated conclusively, significant harmful results have also not been demonstrated. The products provide the opportunity to maintain or enhance palatability while changing macronutrient content to fit nutritional guidelines for minimizing disease risk and obesity.

The demand for such products will continue to motivate food technologists. The opportunity exists for exciting research on the behavioral and physiological consequences of improved substitutes. Research questions come to mind in several areas related to obesity and eating-disorder treatment. Are NNS and fat substitutes helpful in weight-management treatment? Can a food composed of NNS and fat substitutes be developed that could satisfy eating urges and thereby act as a surrogate for junk foods? Could such synthesized snacks be used to reduce compulsive overeating? Do NNS and fat substitutes make it easier for anorexics and bulimics to practice their harmful energy-regulation habits? Will food technology achieve the level of sophistication at which satisfying eating can occur without any nutrition? Will the FDA need to regulate nonnutritive macronutrient substitution in food products to prevent unwary individuals from deviating significantly from dietary recommendations even though they are consuming a wide variety of food products? Can food technologists help the general population cope with the overabundance of food they created? How should products containing low-calorie ingredients be most effectively used? The most meaningful additional research might address the potential effectiveness of low-calorie and low-fat products in weight control when the products are included as part of an overall weight-control program, including behavior modification and exercise. The next several years will provide new research opportunities for exploring the impact of these new technologies on the US diet.

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# Designer Foods: Effects on Development of Cancer[1]

Michael W. Pariza[2]

**ABSTRACT—There are numerous anticarcinogens in the diet. An important question is how to use such substances in an effective, directed way to reduce cancer risk in humans. The "designer foods" concept is one approach for accomplishing this goal. Foods would be engineered to contain effective levels of anticarcinogens. This idea will work only to the extent that there is sufficient scientific knowledge on which to base such food design. Obviously, it is not sufficient simply to extrapolate from animal data to humans. A hypothetical example of the possible "designer fat substitute" is presented and discussed. [J Natl Cancer Inst Monogr 12:105–107, 1992]**

The diet contains many anticarcinogens, ie, substances that reduce cancer risk, that are effective in experimental animals (*1*). Among these are certain vitamins (A, C, E, and the provitamin β-carotene), minerals (calcium, selenium), some forms of fiber, and a wide variety of xenobiotics, ie, chemicals foreign to animal metabolism. An important question is how to use these substances in an effective, directed way to reduce cancer risk in humans.

The "designer foods" concept is one mechanism for accomplishing this goal (*2*). In theory, foods would be specially engineered to contain effective levels of anticarcinogens. They might be designed for people at high risk of developing certain forms of cancer and for the general population. In practice, this idea will work only to the extent that there is sufficient knowledge on which to base the food design.

There are virtually endless numbers of possible designer foods. The simplest example might be a cocktail made from fruits or vegetables known to contain anticarcinogenic factors. Blends like this are already available to the public, although few, if any, were formulated with the idea of reducing cancer risk. In regard to recombinations of existing foods, there should be no objections on scientific grounds. Declaring a specific anticancer health claim on the label is a separate matter that the Food and Drug Administration is grappling with (*3*).

A new set of problems may arise, however, with the proposal to increase the level of a specific dietary anticarcinogen by adding it to a food, as opposed to blending foods that happen to contain the substance. In this case, the distinctions between a *food* and a *drug* may blur, and questions of safety and effectiveness should be anticipated. It is not sufficient simply to extrapolate from animal data to humans. Before an anticarcinogen is seriously proposed for dietary supplementation, it should be subjected to careful study. Among the issues to be investigated are 1) how the anticarcinogen works to inhibit cancer in experimental animals, 2) the relevance of the mechanism of anticarcinogenic action in animals to the development of cancer in humans, and 3) the likelihood that levels of the substance required to effectively reduce cancer risk will be nontoxic in humans. To answer these questions, clinical trials with human subjects may be necessary.

## HYPOTHETICAL EXAMPLE

How might a fat substitute that might also reduce cancer risk be developed? It would be prudent to begin by recognizing that there are three clearly documented effects of fats and fatty acids on experimental carcinogenesis in animals: 1) a general effect related to calorie intake (which affects virtually all types of cancer), 2) enhancement of some forms of cancer by linoleic acid, and 3) inhibition of certain cancers by conjugated dienoic isomers of linoleic acid (CLA) (*4*, *5*).

### Calorie Restriction

Calorie restriction is one of the most powerful known anticarcinogens (*6*, *7*). It is effective against virtually all types of cancer. Moreover, calorie restriction enhances longevity in experimental animals. In contrast, allowing rodents free access to food, as is common practice in most research laboratories, decreases life span and increases cancer incidence. The mechanism of cancer risk reduction by calorie restriction is not yet fully understood, but there is strong evidence implicating hormone imbalance related to ad libitum feeding and resulting obesity. Hormones of particular importance are glucocorticoids (which inhibit the development of cancer at several sites), prolactin (too much of which promotes mammary cancer), and insulin (which acts as a tumor cell growth factor) (*6–10*). Estrogen, when unopposed by progesterone, increases endometrial cancer risk in humans. Excessive adipose tis-

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sue produces estrogen in the bodies of postmenopausal women (*7*).

There is evidence that calorie restriction reduces cancer risk in humans. For example, the low risk of breast cancer in less developed countries undoubtedly relates to calorie restriction during adolescence and puberty (*11*). A problem is that calorie restriction during that time also results in suboptimal growth. This may be undesirable for other reasons: eg, does calorie restriction sufficient to reduce cancer risk also impair brain development? The answers to such questions should be known before implementing drastic dietary changes.

### Specific Fatty Acid Effects

The second fat/cancer issue concerns linoleic acid, the only fatty acid clearly shown to enhance carcinogenesis in rodents. Evidence for this arose first in experiments on fat type. It was found that fats high in certain polyunsaturated fatty acids enhanced carcinogen-induced mammary cancer in rats to a much greater extent than did fats low in such fatty acids. Hence, corn oil enhanced rat mammary cancer more than beef tallow or fish oil. It was then established by Ip et al. (*12*) that the key fatty acid was linoleic acid, an essential fatty acid (fig. 1).

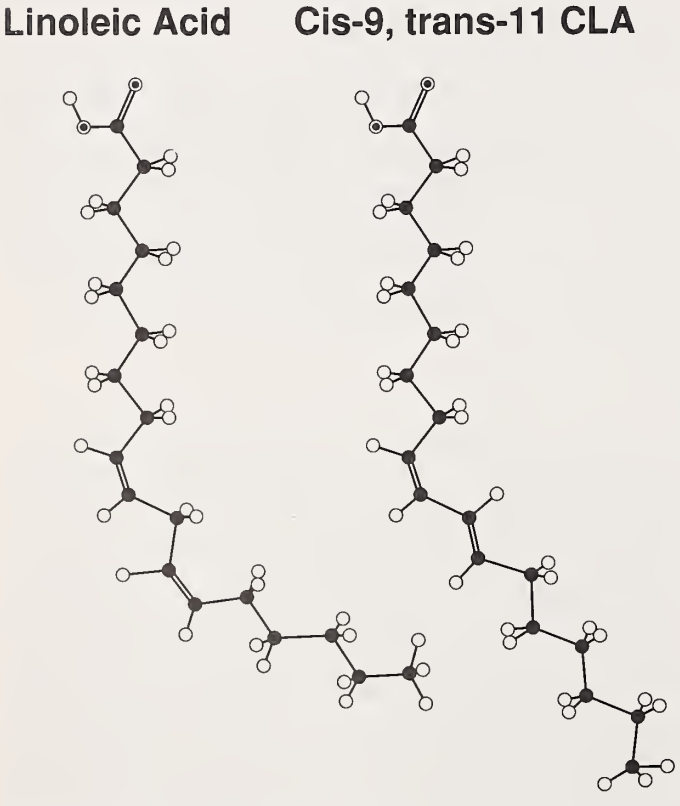


**Figure 1.** Structures of linoleic acid and the *cis*-9, *trans*-11 isomer of CLA © 1991 Food Research Institute; reproduced with permission.

Linoleic acid enhances carcinogen-induced mammary, pancreatic, and probably colon cancer in rodents (*6*). It is the only fatty acid to exhibit such an unequivocal cancer-enhancing effect. Enhancement is seen as linoleic acid is increased up to about 5% of the diet, but no further enhancement of carcinogenesis is observed above this level.

The second specific fatty acid effect concerns CLA, which inhibits carcinogen-induced epidermal and forestomach neoplasia in mice (*4*). As little as 0.5% CLA in the diet significantly reduced carcinogen-induced mammary neoplasia in rats, whereas at 1% in the diet, the maximal effect was observed (*5*). *Cis*-9, *trans*-11 CLA, believed to be the biologically active isomer, is shown in fig. 1.

We have done considerable work to determine how CLA acts to inhibit carcinogenesis in rodents. When consumed by an animal, the *cis*-9, *trans*-11 CLA isomer is taken up and incorporated into cell membrane phospholipid. In the membrane, CLA acts as an antioxidant, protecting other membrane fatty acids from oxidation. Oxidative damage to cell membranes mediated by hydroxyl and other oxygen radicals is thought to be important in the tumor-promotion phase of carcinogenesis.

## DISCUSSION

In conclusion, to develop a fat substitute that might also reduce cancer risk, first, the limits of knowledge should be recognized. Reduced-calorie foods are beneficial and, in some instances, they may even help in reducing cancer. However, major cancer-reduction effects should not be expected. Moreover, if these products are used wisely, ie, with reasonable moderation so as not to induce calorie deprivation in sensitive groups like children, unexpected (and unwanted) side effects should not occur.

Altering the fatty acid composition of fat is a second issue. Based on animal experiments, decreasing linoleic acid might be helpful. Unfortunately, there is little epidemiological support for this conclusion (*11*, *13*). Moreover, linoleic acid is an essential fatty acid that is required for growth and development.

The current diet contains perhaps 0.05% CLA. Given the powerful cancer-inhibiting effects of CLA in rodents, should this be increased? In my opinion, CLA is at the "maybe" stage in terms of human application. Much study, particularly mechanistic, is needed. Also, CLA is under investigation in several laboratories. In time, the results of this work may move CLA into the "fact" category. If this happens, then CLA might form the basis for a fat substitute intended to reduce cancer risk.

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# Prospects for Reducing Virus-Associated Human Cancers by Antiviral Vaccines

Peter J. Fischinger[1]

**ABSTRACT—The last 25 years have seen a major effort to identify human viruses that either cause cancer in humans directly or can be considered significant cofactors or promoters of cancer. The prevailing view is that tumor-associated viruses are necessary but not sufficient for tumor causation. A long latent period between the initial infection and the appearance of the neoplasm is the norm. Generally, the virus implicated as causative is integrated into cellular DNA. Various virus types have been identified; these include both DNA- and RNA-containing agents from the hepadnavirus, herpesvirus, papovavirus, oncornavirus, and lentivirus groups. Although these candidate viral agents are less prevalent in the developed world, hundreds of millions of people are infected worldwide, and about 1 million infected people develop virus-associated tumors annually. Furthermore, nonviral cofactors are suspect or have been identified in the genesis of many virus-associated cancers. A major global approach to prevention of the initial infection can be made by developing efficacious and cost-effective vaccines. An approved human vaccine is available in one case, whereas in every other situation indications exist that a candidate vaccine may soon be available. [J Natl Cancer Inst Monogr 12:109–114, 1992]**

## HISTORICAL CONSIDERATIONS

Transmissibility of animal tumors with cell-free extracts dates back to the last century (*1*). Significant epidemiological, virological, and molecular studies confirm that viruses are directly and indirectly involved in many specific animal tumors. A special class of rare recombinant retroviruses has been shown to be rapidly transforming and comes close to fulfilling the postulates of causality. This group of agents was the first to carry cellular-transforming genes now known as oncogenes. No virus associated with human cancer falls into this category.

Several fascinating observations were made relative to causal relationships of animal or human viruses that were implicated in carcinogenesis. At times, a virus nononcogenic for the species of origin could cause tumors in other species. For example, several human adenovirus types cause tumors in rats and hamsters, but no human tumors are known to be an aftermath of human adenovirus infection. Animal viruses such as feline leukemia virus can infect and readily multiply in human cells in vitro, but neither this virus nor any other oncogenic animal virus is causally involved in human cancer (*2*). The closest transmission of a tumor-promoting animal virus into humans may be human immunodeficiency virus 2 (HIV-2), which by molecular analysis, falls into a subgroup of simian immunodeficiency viruses (*3*). All of the agents described below are human viruses belonging to various groups. These viruses cause human infection and a long-term association with the host generally involving additional cofactors. The tumor is a rare and terminal outcome. Generally, it occurs years or decades after the initial exposure.

## CANDIDATE VIRUSES AND SCOPE OF PROBLEM

Several reviews detailing the status of viruses involved in human cancer have been compiled in the past few years. Many of the references cite past review articles (*4–15*). New molecular advances offer fascinating insights into both the epidemiological phenomena and how malignant transformation might take place. Table 1 details the five major groups of human viruses, the significant neoplasms they are associated with, and an estimate of annual worldwide global incidence.

The first of these is the Epstein-Barr virus (EBV), a member of the large, complex, DNA-containing herpes group of viruses. The potential association of Burkitt's lymphoma, in the tropical hyperendemic malaria belt of Africa, and nasopharyngeal carcinoma, in South China, was already inferred in 1963 and 1971, respectively (*4, 5*). Histologically, typical Burkitt's lymphoma in the United States, however, may not be associated with EBV either epidemiologically or at the molecular level. In nasopharyngeal cancer, the role of EBV is especially important from the prognostic point of view. A recrudescence of an immunological response to the viral capsid antigen of EBV in an individual potentially at risk is a harbinger of an occult neoplasm in the nasopharynx prompting an early evaluation of the patient. Although the number of typical African Burkitt's cases is low, epidemiological data from China and an assessment of Chinese migrants to the United States suggest that about 100 000 cases of nasopharyngeal cancer may occur annually (*16*).

Hepatitis B virus (HBV) is a DNA-containing hepadnavirus of a unique molecular structure and has been impli-

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**Table 1.**—Viruses causally associated with human tumors

| Virus | Category | Neoplasm | Global annual incidence |
|---|---|---|---|
| Epstein-Barr virus | DNA, herpesvirus | Burkitt's lymphoma, nasopharyngeal carcinoma | $\sim 10^5$ |
| Hepatitis B virus (hepatitis C virus) | DNA, hepadnavirus (RNA, flaviviridae) | Primary hepatocellular carcinoma | $\leq 10^6$ |
| Human papilloma virus | DNA, papovavirus | Cervical, anal, penile carcinomas, laryngeal papilloma | $\sim 5 \times 10^5$ |
| Human T-cell leukemia virus 1 | RNA, retrovirus Oncovirinae | Adult T-cell lymphoma, other lymphomas | $\sim 10^4$ |
| Human immunodeficiency virus | RNA, retrovirus Lentivirinae | Kaposi's sarcoma, various lymphomas, other tumors | $10^4$–$10^5$ |

cated in primary hepatocellular carcinoma, which represents one of the end stages of a chronic infection with HBV (*17*). The relative risk factor is about 200:1, and the viral DNA is present in essentially all tumors. Worldwide, there are about 300 million active carriers of HBV, who are identified by an antigenemia with HBV surface antigen. Estimates of between 250 000 and 1 million new cases of primary liver cancer have been made. Because this is a treatment-refractory tumor, these numbers make this cancer, after lung cancer, one of the most lethal global tumors (*6–8*).

Although unrelated to HBV, hepatitis C virus (HCV), a flavivirus type of RNA arbovirus, may emerge as an important contributor to liver cancer. Prevalence rates throughout the world are about 1.5% but in the United States about 50% of the cases of chronic liver disease and primary liver cancer are positive, and in Japan about 75% of primary liver cancer patients are positive for HCV, based on current first-generation tests. In the United States, about 170 000 new cases of HCV occur per year, which is about 25% of all acute hepatitis. A critical point is that about 50% of these patients develop chronic liver disease (*18*). This virus may play a role by itself or may enhance the subsequent development of primary liver cancer in a dual infection with HBV.

Human papillomavirus (HPV), a DNA papovavirus, belongs to a large group of about 60 serotypes widely spread throughout the world. Infections of skin and mucosal surfaces with various types may produce either benign lesions or precursor abnormalities with malignant potential. That infection with several subtypes of HPV, notably 16, 18, 31, and 33, could lead to cervical carcinoma was proposed by Zur Hausen (*9*) in 1977. Penile and perianal cancers also appear to be related to the above subtypes. Other types are involved in warts, condylomata, and conjunctival and laryngeal papillomata (*10*). In terms of prevalence, HPV-16 is the most common, and some investigators estimate that about 35% of all women may be infected with this subtype (*10*). Recent data of sexually active US female university students, with consensus-sequence primer-based polymerase chain-reaction technology, showed a 46% infection rate under conditions where standard tests showed an 11% rate. Of the women showing atypia or dysplasia, 92% were positive (*19*). This is compatible with past estimates of HPV being present in about 80%–90% of cervical carcinoma cells (*11, 20*). Carcinoma of the cervix was estimated by the World Health Organization to be globally the second most frequent malignancy in women, with about 500 000 new cases/year. In certain countries and regions, it is by far the most common female cancer (*11*).

In contrast, human T-cell leukemia virus (HTLV-1) is an RNA-containing retrovirus belonging to the Oncovirinae family. The virus is of recent isolation and has been causally associated with adult T-cell leukemia or lymphoma (*21*). A closely related retrovirus, HTLV-2, has been isolated from hairy cell leukemia, but it is currently unlinked to any particular cancer. HTLV-1 is also linked to non–T-cell lymphomas but not as a directly causative agent, considering molecular data. HTLV-1 is also involved in other diseases, eg, in neurological complications such as peripheral myelopathies and spastic paresis. This virus has a particular focal distribution in southern Japan, the West Indies, and Central Africa. However, smaller foci of infection are present in other geographic sites (*22*). Adult T-cell leukemia is a relatively rare outcome of infection, with lifetime risks of infected individuals developing disease being approximately 1:100 (*12*).

HIV-1 represents a relatively recently identified virus causing a major global pandemic. This is an RNA retrovirus of the Lentivirinae group. AIDS was first defined by the appearance of a rare tumor, Kaposi's sarcoma, in homosexual young men. Interestingly, HIV-1 does not directly cause this tumor because of the absence of HIV-1 genetic material in Kaposi's tumor cells. Incidence of Kaposi's sarcoma is on the wane; early in the epidemic, over 20% of all diagnoses of AIDS were due to Kaposi's sarcoma, but now only about 11% (*23*). Various lymphomas are the next highest manifestation of neoplastic sequelae of HIV infection. At the end of 1990, lymphomas were found in about 3% of AIDS cases (*23*). As intermediary therapies prolong life after the initial AIDS diagnosis, new data suggest that the incidence of these and other tumors may be rising significantly in long-

term survivors, so that already in 1992, about 14% of the 36 000 cases of non-Hodgkin's lymphoma in the United States will be related to HIV-1 infection (*24*).

## MECHANISMS AND COFACTORS

The presence of viral genetic information in the tumor cell is the norm by which a causal relationship is established. Some of the major features are described in table 2. EBV can immortalize and polyclonally expand B lymphocytes, where the viral DNA exists in an episomal form, whereas essentially all cases of endemic Burkitt's lymphoma have an integrated EBV genome in the monoclonal tumor cell. Three major types of translocation occur with the well-known activation of the *myc* oncogene in the tumor cell. High levels of antibody exist to viral capsid antigens, and a rise in titer is predictive of a tumor onset. In sporadic Burkitt's lymphoma cases, only about 20% carry the EBV DNA, indicative of additional possible causes. Undifferentiated cancer of the nasopharynx is also monoclonal and similar to Burkitt's lymphoma in that multiple copies of EBV DNA are present in the epithelial tumor cells. In this tumor, the rise of IgA antibody to viral capsid antigen is highly prognostic and has been used extensively as an early screening method (*4, 5*).

In both cases, cofactors are apparently required. In endemic Burkitt's lymphoma, the standard malaria infection is both immunosuppressive and stimulative of B-lymphocyte proliferation, which, at the least, increases the target-cell population in which a final chromosomal translocation occurs. Second, malaria episodes depress the function of specific T lymphocytes that control EBV-infected B-lymphocyte growth. Although several cofactors have been implicated in the genesis of nasopharyngeal cancer, the strongest link is the consumption of salted fish early in life (*25*).

HBV does not possess a known oncogene, but its DNA is found integrated in 90% or more of liver cancer cases. However, the fourth gene of HBV, ie, the X gene, has been shown to transactivate heterologous viral gene sequences (*26*). A developmental stochastic model postulating a less differentiated replicating precursor cell that proliferated extensively after HBV infection was proposed by Blumberg (*6*). A secondary fixative event was also a part of the process. Cofactors that are toxic to liver cells, eg, alcohol, and more typically known carcinogens, eg, aflatoxin, have been invoked on many occasions. Most recent data suggest that primary hepatocellular carcinoma arising subsequent to HBV infection may be due to an inactivation of a tumor-suppressor gene, p53, based on mutations in a critical part of the p53 DNA (*27*).

HPV also integrates in the DNA of cervical cancer cells, whereas the viral DNA is episomal in premalignant conditions. Integration is tumor specific and monoclonal. The dissection of HPV early genes (E1 to E7) has been well worked out in the immortalization of keratinocytes. Viral DNA is transcribed and E6 and E7 genes, especially, both of which are needed for full transformation, are regularly expressed (*28*). Findings by Dyson et al. (*29*) and Werness et al. (*30*) elegantly demonstrate that HPV 16 and 18 E7 oncoproteins bind the retinoblastoma tumor-suppressor gene product, and the E6 proteins bind to the p53 tumor-suppressor gene protein. In this case as well, cofactors must play a role. Curiously, heavy tobacco use has been implicated in anogenital cancers and in its more proximal target organs (*11, 31*).

HTLV-1 genomic information is present as proviral DNA in essentially all adult T-cell lymphomas that are monoclonal, and antibodies to HTLV-1 are regularly detected. HTLV-1 has a unique open reading-frame coding for a transactivating protein. Although there is no counterpart sequence in mammalian cell DNA, the sequence can act as an oncogene, as demonstrated by transgenic mouse experiments (*32*). The current understanding is that its nuclear protein activates the promoter for the interleukin-2 receptor and that an activation of the autocrine stimulatory loop occurs in conjunction with the

**Table 2.**—Viral mechanisms and cofactors involved in cancer development

| Virus | Mechanisms | Probable cofactors |
|---|---|---|
| Epstein-Barr virus | Expansion of B lymphocytes, episomal and integrated DNA, immortalization, C-myc activation, immune depression | Hyperendemic malaria, salted fish in childhood, exposure to smoke |
| Hepatitis B virus | Integration of viral DNA, cell proliferation, transactivation, inactivation of tumor-suppressor genes | Aflatoxins, alcohol, smoking |
| Human papilloma viruses | Immortalization, episomal and integrated DNA, early genes inactivate cellular tumor-suppressor genes | Smoking, natural carcinogens, coinfections, solar exposure, x rays |
| Human T-cell leukemia virus 1 | Immortalization, transactivation, oncogene-like action | Microfilaria (?) |
| Human immunodeficiency virus 1 | Immune depression, transactivation, polyclonal B-lymphocyte activation, aberrant growth factor release | Life-style, coinfections |

T-cell receptor. No obvious cofactors have been implicated for adult T-cell lymphoma development (*12*).

HIV and other lentiviruses are not directly tumorigenic, despite a complex of nine additional nonstructural genes. Many of these accessory genes function in viral autoregulatory loops, but several genes, eg, the transactivating gene, can affect distant genes and cellular protein expression. The principal target cells for HIV-1 infection are the T4 lymphocytes and the macrophage series of cells. Progressive destruction of T4 lymphocytes results in an erosion of the immune system. Neither Kaposi's sarcoma cells nor the various lymphomas that arise postinfection contain HIV-1 proviral DNA. Presumably, the main effects of the virus are aberrant growth factor stimulation and a loss of normal immune surveillance. These tumors may be provoked by secondary unidentified infectious agents (*14*).

## VACCINES AGAINST HUMAN TUMOR-ASSOCIATED VIRUSES

A summary of the status of vaccine development is detailed in table 3. Based on the successful field vaccine against herpesvirus-induced Marek's disease of chickens, the development of a subunit vaccine against EBV is quite advanced (*33*). A membrane antigen glycoprotein of 340 000 $M_r$ that induces virus-neutralizing antibodies was a likely choice. There is only one animal model in which EBV induces tumors, ie, the rare cotton-top tamarin monkey. When administered with strong adjuvants, the vaccinated tamarins develop high-titer antibodies against EBV gp340 that are strongly neutralizing. When challenged with a very high 100% tumor-inducing virus dose, most of the animals withstood infection and none developed tumors. These results should facilitate human phase I trials in select groups, presumably in areas where there is a high probability of developing nasopharyngeal cancer or Burkitt's lymphoma (*34*).

Two generations of a safe and effective vaccine that prevents infection with HBV are in use. The preparations are either the native HBV surface glycoprotein antigen organized in 22-nm particles or the analogous yeast cell-engineered surface antigen material. However, some of the vaccines do not achieve protective immunity. Other regions of the HBV virus also play an important role in generating a high level of protection. The pre-S1 and pre-S2 domains and even the internal core proteins could induce protection. These are involved in helper T-cell responses and recall functions. Because HBV transmission takes place perinatally or early in life and transmission at that time has the highest probability of resulting in an HBV chronic carrier state, vaccination must take place soon after birth. Coadministration of passive anti-HBV antibodies with a vaccine has proved to be most effica-

**Table 3.**—Overview of vaccines against human tumor-associated viruses*

| Virus | Vaccine preparation | Model system | Immune responses | Protection from infection | Protection from disease | Human trial status |
|---|---|---|---|---|---|---|
| Epstein-Barr virus | gp340 | Cotton-top tamarin | High-neutralizing antibody | Yes, but incomplete | No tumors | Poised for phase I |
| Hepatitis B virus | Plasma HBs (surface antigen), yeast-derived HBs | Human | Protective antibodies | Almost complete | Must wait | Phase III, third-generation vaccine pending |
| Human papilloma virus | *1* Purified virions, subunits | Bovine (uses bovine papillomavirus as challenge) | High-neutralizing antibodies | Yes | Not applicable | Not ready |
| | *2* Early antigens, engineered | | Not assessed | Protection on challenge with tumor cells | Retards tumor progression | |
| | *3* Transformed cells | | Variable | None | None | |
| Human T-cell leukemia virus 1 | Subunit proteins from producer cell lines | Pig-tailed macaque (uses STLV-1 as challenge) | Humoral and cellular responses ADCC | Complete protection | Not applicable | Not ready |
| Human immunodeficiency virus 1 | *1* Native gp120<br>*2* Engineered gp120–160<br>*3* Infectious recombinant vaccinia with gp160 | Chimpanzee | Neutralizing antibody<br>ACC<br>ADCC | Can protect from homologous type | Not applicable in chimpanzees | Phase I or II trials for *2* and *3* safe |

*HBs, hepatitis B surface; STLV-1, simian T-lymphotropic virus 1; ADCC, antibody-dependent cell-mediated cytotoxicity; ADC, antibody-dependent complement-mediated cytotoxicity.

cious. Despite the fact that liver cancer develops 20–40 years after initial infection, a positive indication in vaccine trials can be achieved rapidly. Primary hepatocellular cancer occurs classically in virus carriers with various levels of chronic hepatitis, necrosis, and cirrhosis. Accordingly, protection from infection and the lack of chronic viremia should indicate long-term beneficial effects soon after vaccination (*6, 17, 35*).

Attempts at vaccination against HPV have not been made; however, a series of experiments with the bovine papillomavirus (BPV) system are promising. In cattle, various kinds of BPV-induced papillomas are common, as are carcinomas that arise from these papillomas in the presence of cofactors. Vaccinations were performed in calves with native virus, infectious recombinant vaccinia virus containing early protein-coding genes, or tumor-extract preparations. Pure BPV or its proteins induced high levels of specific neutralizing antibody that completely protected calves from papillomas after a high-titer ($10^{12}$ particles) challenge in scarification (*36*). Rats were exposed to recombinant infectious vaccinia viruses expressing early proteins E1, E2, E5, E6, and E7. Challenge was performed with syngeneic BPV-transformed rat cells. Subsequent tumor growth was abolished or retarded only in vaccines that expressed E5, E6, and E7 proteins (*37*). Finally, BPV-generated tumor extracts or BPV-transformed cells were used to immunize calves. High-titer neutralizing antibody was induced with tumor extracts. When homologous-type BPV was used as a challenge, two of three calves that received tumor extract were protected. No protection was seen in calves receiving the transferred cell vaccine (*37*).

HTLV-1 has close ($\geq$90% homology) simian virus relatives (STLV-1) that are linked to lymphomas and leukemias in monkeys and higher primates. In analogy with the relatively successful feline leukemia virus vaccine, macaques were vaccinated with HTLV-1–soluble proteins released from a serum-free HTLV-1–producing cell line. Serological responses were observed and strengthened on challenge. Antibody-dependent complement-mediated cellular cytotoxicity was observed against both HTLV-1– and STLV-1–infected target cells. Challenge occurred with an STLV-1–producing cell line. The vaccine protected macaques from STLV-1 infection, whereas all control animals became infected (*38*).

A vaccine against HIV-1 presents a considerable challenge because of virus strain variability, lack of a known protective response, and an imperfect animal model (*14*). Based on other retrovirus models, the major target for a vaccine was the external major viral glycoprotein complex (gp160, which gives rise to gp120 and gp41). Precise molecular dissection identified more than 20 important sites related to virus type- and group-specific humoral and cellular immune responses. Native HIV-1 glycoprotein, infectious vaccinia recombinants expressing gp160, and genetically engineered gp160 or gp120 produced in various molecular vectors were used as vaccines in chimpanzees. This species is readily infected by HIV-1, but the infection does not progress to AIDS. Parallel experiments in the simian system STLV-1 showed some early positive results (*15*). With all three HIV-1 vaccine forms in chimpanzees, earlier data indicated that none could protect, even from homologous-type HIV-1 challenge. Several recent experiments, however, with larger amounts of genetically engineered gp120, which generated good responses including high neutralizing antibodies, demonstrated protection from primary infection with homologous HIV-1 type (*15*). Whether cross protection is possible in the chimpanzee must be explored. In parallel experiments, human volunteers were inoculated with baculovirus vector-derived gp160 of a single strain of HIV-1. This vaccine appears to be safe in humans, and both humoral and cellular immune responses were noted (*15*). However, it is too early to assess whether this vaccine could protect against either infection or disease.

## CONCLUSIONS

Despite the fact that virus-associated cancers are a relatively minor problem in the United States, global cancer can be greatly ameliorated by timely vaccine intervention. Several major lethal human cancers could be greatly reduced in scope. The most significant of these, primary liver cancer, is amenable to large-scale interventions. It is gratifying that, based on model systems, each viral pathogen may be prevented by various vaccine preparations. As the world faces a second decade of the AIDs pandemic with its devastating consequences, one of which is the ever-increasing incidence of secondary neoplasms, critical efforts at prevention are even more compelling.

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# Tumor-Susceptibility Markers

**Dominique Bellet**[1,2]

**ABSTRACT—Genetic analyses of unusual hereditary cancers and of common neoplasms suggest that tumorigenesis proceeds through a series of genetic alterations involving oncogenes and tumor-suppressor genes. Such genes can be viewed as tumor-susceptibility genes, and DNA tests that examine them might be useful in determining an increased risk of cancer development before the onset of a tumor. Indeed, DNA tests have already proved useful in the genetic counseling of families with an increased risk of rare inherited diseases such as retinoblastoma, multiple endocrine neoplasia type 2a, or Li-Fraumeni syndrome. The current investigation of these familial disorders is enabling the development of expertise, reagents, and methods that will eventually focus on the most common cancers. In assessing risk for these common tumors, several genes will probably require study to achieve more accurate prediction of cancer risk. For example, genetic abnormalities of the *ras* oncogene and of either the retinoblastoma gene (Rb) or the p53 tumor-suppressor gene have been found in many tumors and appear to be particularly important in the study of individuals at increased risk of lung, breast, or colon cancers. In addition, the study of tumor-associated markers that might already be detectable in the preneoplastic state can be carried out in parallel with tests that search for evidence of mutations in tumor-susceptibility genes. Finally, both classes of markers might be complementary in genetic counseling or screening of populations at increased risk. However, the capacity for detecting tumor-susceptibility markers creates a responsibility for the physician in terms of the proper use of this information. [J Natl Cancer Inst Monogr 12:115–121, 1992]**

Tumor-associated markers such as α-fetoprotein, human chorionic gonadotropin, and CA 19-9 have proved to be useful in the detection and, especially, the follow-up of established tumors (*1*). However, the onset of a malignant tumor is preceded by 10–30 silent years, and the multistage model of carcinogenesis suggests that both environmental and hereditary factors contribute to the development of neoplasia during this silent period (*2, 3*). For most tumors, it is difficult to assess the respective contribution of either the genetic background or the environmental factors in tumorigenesis, but it is generally agreed that both factors contribute to the accumulation of genetic changes in a single cell. Indeed, direct analysis of specific gene lesions in an extensive array of human tumors has indicated that cancer is the result of an accumulation of discrete genetic changes in the cell genome occurring over an extended period (*4*). These genetic alterations include the somatic activation of cellular oncogenes through point mutation, rearrangement, or amplification (*5*) and the germ-line or somatic inactivation of tumor-suppressor genes through point mutation or deletion (or both) (*6, 7*). The analysis of these genetic alterations during the decades preceding the emergence of a malignancy might be useful in assessing an increased risk of cancer. Thus, it appears that, in addition to tumor-associated markers that are gene products, another class of tumor marker, ie, tumor-susceptibility markers, can be defined (fig. 1). The latter markers comprise susceptibility genes, and the main purpose of this article is to examine the usefulness of studying these genes so as to establish an increased risk of cancer development. In particular, I focus on susceptibility genes of established or potential interest in the screening of two groups, those individuals belonging to families with rare hereditary cancers, and the many people likely to develop the most frequent cancers (*8*).

## TUMOR-SUSCEPTIBILITY MARKERS AND FAMILIAL TUMORS

Genetic analysis of several unusual childhood tumors, as well as of common adult neoplasms, has suggested that the cancer phenotype is broadly determined by two classes of genes, oncogenes and tumor-suppressor genes, which are functionally opposed. Oncogenes, though diverse in function, appear to exert control over cellular replication and differentiation, and deregulated expression of oncogenes participates in cellular transformation. Moreover, evidence from experiments with primary rodent cells indicates that the expression of two or more independent oncogenes is required for tumorigenic transformation in vitro, giving rise to the concept of oncogene cooperation in tumorigenesis (*4*).

The tumor-suppressor genes, also designated *regulatory* genes (*9*) or *antioncogenes* (*10*), have been postulated to encode proteins that regulate normal growth and, thus, indirectly suppress neoplastic development (*11*). In cells, these genes may act recessively, so that both maternal and paternal copies of the gene product must be inactivated for the suppressor function to be eliminated. This model for tumor-suppressor genes was originally postulated by Knudson (*12*) and has gained support from the study and

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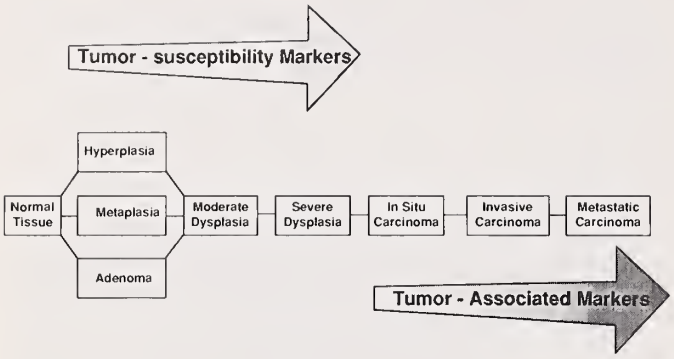


**Figure 1.**—Tumor markers and tumorigenic process. Tumor-susceptibility markers comprise susceptibility genes, the study of which may be useful for determining increased risk of cancer development during 10–30 silent years preceding tumor onset. Tumor-associated markers comprise gene products, the determination of which has proved useful for diagnosis and, in particular, follow-up of established tumors.

molecular cloning of the retinoblastoma gene (Rb) on chromosome 13q (*13*). In hereditary tumors, according to Knudson's hypothesis, one mutation is inherited via the germinal cells and the second occurs in somatic cells, whereas in nonhereditary tumors, both mutations occur in somatic cells.

Indeed, the class of genes most strongly associated with familial tumors is that of tumor-suppressor genes (*14*). Mutations that knock out tumor-suppressor genes may be just as important in causing cancer as activation of oncogenes, and mutations in tumor-suppressor genes can be viewed as tumor-susceptibility markers of familial tumors. Allelic deletion coupled with mutation of the remaining allele is a theoretical hallmark of tumor-suppressor genes, and frequent detection of allelic loss at specific chromosomal regions implicates these regions as sites of putative tumor-suppressor genes.

The chromosome locations of candidates or established tumor-suppressor genes in inherited cancer syndromes and in hereditary cancers are presented in table 1. In certain malignancies, eg, retinoblastoma, loss of function of only a single tumor-suppressor gene is implicated. In other malignancies, eg, medullary thyroid carcinomas, few genes appear to be important causative factors. In contrast, studies of colorectal cancers that develop in patients with familial adenomatous polyposis (FAP) have indicated that loss of multiple tumor-suppressor genes and expression of oncogenes may be necessary for progression to a fully malignant condition. These observations imply that cell-cycle controls may vary from one cell type or organ to another. As a consequence, one or more tumor-susceptibility genes should be studied in individuals with an inherited predisposition to cancer development to determine the increased risk in a given relative.

## TUMOR-SUSCEPTIBILITY MARKERS AND MOST FREQUENT CANCERS

Knudson (*12*) has suggested that a mutation in an inherited cancer-susceptibility gene may be the first step in a recessive change in the tumor cells and that the same gene may be involved in both familial and nonfamilial cases of a given tumor. At the cellular level, there is probably little to distinguish the mutations in inherited and sporadic diseases, and tumor-suppressor genes previously presented as being tumor-susceptibility markers of familial cancers might also be viewed as such for the most frequent sporadic cancers.

The chromosome locations of either candidate or established tumor-suppressor genes in the most frequent worldwide cancers are presented in table 2. The five most frequent tumors (ie, cancers of the stomach, lung, breast, colon, rectum, and cervix) account for almost 50% of all malignancies, whereas the eleven most frequent tumors account for 72% of all cancers (*8*). In these frequent

**Table 1.**—Inherited cancer syndromes, hereditary cancers, and locations of either established or candidate tumor-suppressor genes*

| Inherited predisposition | Chromosome location | Refs. |
|---|---|---|
| Neurofibromatosis type 1 (NF1) | 17q21 (NF1) | *36* |
| NF2 | 22q11 (NF2) | *37, 38* |
| Multiple endocrine neoplasia type 1 (MEN 1) | 11q | *39* |
| MEN 2a | 1p, 10 | *39, 40* |
| Von Hippel-Lindau | 3p | *39* |
| Li-Fraumeni | 17p13 (p53) | *14, 30* |
| Familial adenomatous polyposis (FAP) | 5q, 17p (p53), 18q21 (DCC), 22q11 (NF2) | *41* |
| Medullary thyroid carcinoma | 1p, 10 | *17, 40* |
| Wilms' tumor | 11p13 (WT1) | *42* |
| Retinoblastoma | 13q14 (Rb) | *13* |

*Chromosome locations were mapped by family linkage analysis, RFLP studies, or direct analysis of the tumor-suppressor gene. Names in parentheses are established or candidate tumor-suppressor genes, including the retinoblastoma gene (Rb) on chromosome 13q14, the p53 gene on chromosome 17p13, the Wilms' tumor gene on chromosome 11p13, the DCC gene on chromosome 18q21, the neurofibromatosis type 1 gene (NF1) on chromosome 17q21, and the NF2 gene on chromosome 22q11. (*39*; original data cited in this article.)

**Table 2.**—Chromosome locations of either established or candidate tumor-suppressor genes in most frequent worldwide cancers*

| Cancer | Rank | Chromosome location | Refs. |
|---|---|---|---|
| Stomach | 1 | 1p, 1q, 12p, 13q | *43* |
| Lung | 2 | 3p, 13q (Rb), 17p (p53) | *21, 25, 26, 44–47* |
| Breast | 3 | 1p, 1q, 3p, 11p (WT1), 13q (Rb), 16q, 17p (p53), 17q (NF1), 18q (DCC) | *47–51* |
| Colon/rectum | 4 | 1q, 4p, 5q, 6p, 8p, 9q, 17p (p53), 18q (DCC), 22q (NF2) | *3, 7, 29, 33, 47, 52–57* |
| Cervix | 5 | 11p (WT1), 17P (p53) | *43, 47* |
| Esophagus | 7 | 17p (p53) | *34* |
| Liver | 8 | 4q, 5q, 8q, 10q, 11p (WT1), 13q, 16q, 17p (p53) | *58–63* |
| Prostate | 10 | 10q, 13q (Rb), 16q | *64, 65* |
| Bladder | 11 | 9q, 11p (WT1), 13q (Rb), 17p (p53) | *46, 47, 66* |

*Cancers are ranked according to their worldwide frequency (*8*). Chromosome location of tumor-suppressor genes was assigned as in table 1.

cancers, it is striking that many tumor-suppressor genes can be implicated in their tumorigenesis. Some tumor-suppressor genes, eg, p53 on chromosome 17 or Rb on chromosome 13, appear to be inactivated in multiple common tumor types, whereas others may be inactivated in a specific tumor type. Moreover, the genetic model for colorectal carcinogenesis described by Vogelstein (*15*) implicates genetic alterations other than tumor-suppressor gene mutations or deletions. In that model, the *ras* gene mutation may be the initiating event, at least in a subset of colorectal tumors, and the progressive accumulation of genetic changes in both oncogenes and tumor-suppressor genes parallels the clinical progression of colorectal tumors from normal epithelium to benign tumors and further to the malignant stage of the disease.

These events need not be the same in all cases or occur in the same order, and, although the genetic alterations occur according to a preferred sequence, it is not the time of occurrence of mutations or their order but rather their accumulation that is most important in tumor development (*3, 15*). The relevance of the colorectal model to other frequent tumor types, eg, bladder cancers and breast tumors, is beginning to gain support. These findings have practical implications: 1) several tumor-susceptibility markers (oncogenes or tumor-suppressor genes) will probably need to be studied in individuals at risk for the most frequent cancers; 2) looking at several genes instead of just one may give a more accurate prediction of cancer susceptibility in a defined individual; and 3) DNA tests that can be used in clinical practice need to be developed.

## CURRENT TESTS TO DETECT GENETIC ALTERATIONS

The realization that as many as 10 distinct mutations need to accumulate in a cell before it becomes cancerous implies that researchers or biologists must examine several tumor-susceptibility genes to assess the increased risk of tumor development; this raises the question of the capacity of current laboratory tests to detect several genetic alterations in many samples. Some current tests to detect genetic alterations are presented in figure 2. Indeed, the labor-intensive nature of cytogenetic analysis prohibits screening many tumors. Similarly, the original NIH/3T3 transfection assay used to identify oncogenes (eg, altered *ras* genes) was not suitable for analysis of many samples, mainly due to the laborious nature of the assay (*16*). However, this assay did help to reveal the positions at which point mutations occurred and therefore opened up the possibility of analyzing the alterations directly in the tumor DNA (*see* below). Restriction-fragment-length polymorphism (RFLP) analysis has already proved clinically useful for genetic screening of individuals at risk of a familial cancer syndrome, eg, multiple endocrine neoplasia type 2a (MEN 2a) (*17*).

Because Southern or Northern hybridization with large probes may not always detect subtle alterations, eg, small deletions or rearrangements, or point mutations, more sensitive molecular assays have been developed. Point mutations are usually detected by selective hybridization with synthetic oligodeoxynucleotide probes that are specific for known mutations (*18, 19*). By using probes specific for a defined mutation in such an oligodeoxynucleotide hybrid-

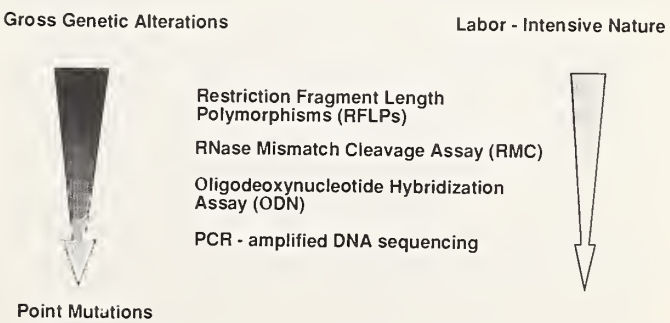


**Figure 2.**—Current tests to detect genetic alterations. These tests are classified according to either their increasing sensitivity or their decreasing labor-intensive nature. PCR, polymerase chain reaction.

ization assay (ODN), the exact base-pair change can be identified.

Alternatively, the position of a mutation can be detected by RNase mismatch cleavage (RMC) (*20*), which uses an RNA probe that forms a mismatched hybrid with the mutated DNA. RNase A cleaves the RNA at the position of the mismatch, resulting in two fragments that can be identified after gel electrophoresis. However, ODN is only sensitive for defined mutations but is more sensitive than RMC; indeed, the RNase protection assay has a detection rate of less than 50% for single-pair mutations (*21*). Both methods make use of DNA, which can be isolated from fresh tissue or lymphocytes or from frozen and paraffin-embedded tissue sections and from which the relevant sequences are amplified in vitro by the polymerase chain reaction (PCR) (*22, 23*).

Finally, PCR amplification of either genomic DNA or reverse-transcribed RNA followed by sequence analysis can also be used to determine mutations (*14, 24, 25*). Simple immunohistochemical methods should also be used for detecting the products of mutated genes such as p53 (*25*). However, screening tests to determine such mutations cannot rely on methods that assume that the mutations will result in high levels of mutant protein (*14*). For example, intronic point mutations can lead to the production of abnormal or no p53 protein that may or may not be detected by immunohistochemical methods (*26*). Finally, research on both oncogenes and tumor-suppressor genes has been restricted to modest-size laboratory studies, but assays have now reached the point at which large clinical and population-based studies appear feasible.

## DNA-BASED DIAGNOSIS AND GENETIC COUNSELING

Recent advances in molecular biology have opened the door for DNA-based diagnosis of many human genetic disorders. These advances have been applied to the genetic counseling of families at risk for either hereditary cancers or familial cancer syndromes, eg, retinoblastoma (*27*), medullary thyroid carcinoma (*17*), MEN 2a (*17, 28*), FAP (*29*), and Li-Fraumeni syndrome (*14, 30*). With a sensitive technique of primer-directed enzymatic amplification followed by DNA sequence analysis, it was demonstrated that this technique can distinguish hereditary from nonhereditary retinoblastoma and is useful in risk estimation and genetic counseling (*27*). RFLP analyses with DNA probes tightly linked to the gene for susceptibility to MEN 2a (RBP3, MCK2, and TBQ16) have proved much more useful in predicting the carrier state than the conventional endocrine challenge, which involves pentagastrin stimulation followed by a calcitonin assay (especially in younger people), but accuracy was maximal when both methods were used (*17, 28*).

Indeed, the estimated residual risk to an individual with a negative biochemical screen, with pentagastrin stimulation and the best available calcitonin radioimmunoassay, decreases substantially with age from late childhood but has not been shown to fall below 7% (*27*). Although this figure may be improved by more sensitive calcitonin assays (*31, 32*), genetic tests to determine a carrier status were found to be more accurate: the inheritance of a low-risk RBP3 allele points to a residual risk at birth of about 3%. Finally, the 3% risk with RPB3 alone decreases to less than 1% by age 30 years if combined with a negative pentagastrin-stimulated calcitonin test (*28*). These examples of DNA tests, considered as representative, demonstrate that DNA-based diagnosis is critical for genetic counseling and for early clinical intervention in families of patients. Moreover, the availability of accurate DNA markers for tumor-susceptibility genes (eg, MEN 2a) introduces the possibility of providing prenatal diagnosis for either familial cancer syndromes or hereditary cancers (*28*).

## DNA TESTS, IMMUNOLOGICAL ASSAYS, SCREENING, AND TUMOR TREATMENT

The current investigation of relatively rare familial disorders such as MEN 2a is enabling the development of expertise, reagents, and methods that will eventually focus on more common cancers such as those of the lung, breast, and colon. As already discussed, these carcinomas probably arise from a minimum of five or more genetic alterations, and several DNA tests will have to be carried out to identify an increased risk of cancer development. However, the study of genetic alterations affecting genes such as *ras*, Rb, or p53 might be particularly warranted: *ras* gene mutations have been found in 20%–30% and 50%–60% of lung and colon cancers, respectively, and such mutations may be the initiating event in a subset of colorectal tumors. Rb mutations have been described in 40% and 20% of lung and breast cancers, respectively, and it is apparent that the loss of Rb function has a central role in the initiation and/or the progression of many human cancers.

Finally, several features justify a careful examination of the p53 gene. Indeed, p53 mutations are present in 50%–70% of both lung and colon cancers and in 50% of breast cancers, and the p53 gene is currently the most commonly altered gene identified in human tumors, occurring in a large fraction (perhaps even half) of the total cancers in the United States and United Kingdom (*15*). Moreover, at least in colorectal tumorigenesis, p53 mutations seem to occur near the transition from benign to malignant growth, and p53 gene alterations play an important role in this progression (*33*). Interestingly, the identification of aberrant p53 gene alleles in 35% of esophageal cancers and the effectiveness as mutagens of tobacco and certain *N*-nitrosamines (two types of exposures linked to an elevated risk of esophageal tumors) suggest that one relevant site of DNA damage in this cancer might be the p53 gene locus (*34*). Taken together, these observations suggest that investigation of the *ras*, Rb, and p53 genes in certain populations with a high risk of cancer, eg, heavy smokers, would be useful. As pointed

out by Marx (*35*), "if indeed you need 10 or 15 [gene] hits and you could pick up people when they have only one or two, that would be pretty important clinically." These individuals may be encouraged to stop cigarette smoking that might produce the additional mutations that would propel their cells into malignancy.

In addition to performing DNA tests for assessing tumor-susceptibility markers in populations at exceptionally high risk, it might also be useful to carry out immunological assays to measure tumor-associated markers in parallel. In effect, the latter markers may already be present in a preneoplastic state. For example, carcinoembryonic antigen (CEA), a widely known tumor-associated marker, is a gene product expressed at low levels in normal colon tissue; its expression gradually increases from normal epithelium to adenomas and further on to carcinomas (*36*). It has been shown that CEA functions as an intercellular adhesion molecule (*37*), and the DCC gene that is deleted in colon carcinoma is likely to also code for a cell-adhesion molecule (*29*). The biological function of some cell-adhesion molecules is probably critical in tumor development, and it might be valid to look at both susceptibility genes (eg, DCC) and tumor-associated markers (eg, CEA) to obtain more accurate predictions of cancer susceptibility.

## CONCLUSIONS

In fact, recent advances in molecular genetics already enable the genetic counseling of families with increased risk of rare hereditary cancers such as retinoblastomas. Although the study of a cancer-susceptibility gene may not always result in a direct benefit to the individuals, preventive measures that can be taken render such information of immediate value. However, the usefulness of DNA tests for the counseling or screening of particular populations with an increased risk of cancers (eg, lung tumors in smokers) remains a "maybe." Indeed, several DNA tests assessing various tumor-susceptibility genes will probably need to be performed in parallel with immunological assays on relevant tumor-associated markers and other surveillances (eg, physical examinations, mammography, and Pap smears) to achieve better prediction of cancer risk in these populations. The clinical value of DNA tests for the screening of the general population will probably continue to be an unfounded rumor for a long period. Finally, in assessing the usefulness of genetic screening, distinguishing reality from theoretical possibility may be difficult for both the clinician and the patient because of the publicity given to new advances in the search for such markers. Moreover, it is clear that the ability to detect tumor-susceptibility markers creates a responsibility for the physician in terms of the use of this information. Thus, further work should be rapidly undertaken to determine both the usefulness and the limitations of tumor-susceptibility markers in clinical practice.

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# Identification of Cancer-Prone Individuals: p53 and Family Cancer Syndromes

Lisa Diller *and* Stephen H. Friend[1,2]

**ABSTRACT—Progress in prevention of any disease is enhanced by the identification of a group of individuals who are at increased risk to develop the disease. The ability to detect families with evident predisposition to malignancy provides a unique opportunity to study high-risk groups. Recent studies of the p53 gene have suggested that heritable mutations in this gene may predispose affected individuals to the development of a wide variety of tumors. In this article, evidence for the involvement of p53 in inheritable cancers is assessed, and the implications for future studies are discussed. [J Natl Cancer Inst Monogr 12:123–124, 1992]**

The role of mutations in tumor-suppressor genes in the development of malignancy has been extensively evaluated in recent years. Both the retinoblastoma gene (Rb) product and p53 suppress cellular growth and are found to be abnormal or deleted in many different types of tumors. Deletions and mutations of Rb have been found in retinoblastomas, as well as in breast carcinomas, sarcomas, and small-cell lung and bladder cancers (*1, 2*). Clinical observation of families with an inherited tendency to develop tumors supports Knudson's (*3*) "two-hit" hypothesis, first proposed in 1971 to explain familial retinoblastoma. This hypothesis predicts that a mutation in a single allele is inherited in the germ line, and a "second hit," or loss of the other normal allele, occurs only in the tumor as it develops, thus rendering the tumor cells completely deficient in an important growth-controlling protein. In recent years, it has been demonstrated in several laboratories that the p53 gene is a growth-controlling gene and that many sporadic tumors, including breast cancer, leukemias, osteosarcomas, brain tumors, and colon carcinomas have mutations in p53 (*4–6*). This has led us and others to test the hypothesis that germ-line mutations in the gene encoding p53 may account for the familial forms of some of these tumors.

The Li-Fraumeni syndrome (LFS) is a rare condition in which affected family members develop many different types of tumors. The syndrome was first described in 1969 by Li and Fraumeni (*7*), who noted four kindreds with children with sarcoma in which a first-degree relative also developed sarcoma. Other members of these families also had a higher-than-expected incidence of breast cancer and other neoplasms. LFS is now defined as a kindred in which a proband develops sarcoma at less than 45 years of age and has at least two relatives with malignancies. The syndrome has since been identified in approximately 200 families worldwide. In addition to sarcoma and breast cancer, members of these families have a significantly increased risk for the development of other characteristic malignancies, including leukemia, brain tumors, osteosarcomas, and adrenocortical carcinomas. These malignancies are characterized by early-onset, bilateral disease in paired organs, or multiple primary tumors in an individual's lifetime (*8*). Classic genetic analysis predicts an autosomal-dominant mode of inheritance with incomplete penetrance (*9, 10*).

In the search for the genetic etiology of LFS, researchers have turned to the gene encoding p53 for several reasons. First, given the strong association between tumor-suppressor genes and familial cancers, a tumor-suppressor gene is a likely candidate gene in this syndrome. Many of the types of tumors seen in the LFS families, ie, sarcoma, leukemia, brain tumors, and breast cancer, are associated with p53 mutations when they occur in their sporadic forms (*4, 5*). Finally, transgenic mice carrying a mutant p53 allele develop lymphoid tumors, osteosarcomas, and adenocarcinomas (*11*), a group of tumors similar to those seen in the LFS families. For these reasons, p53 was chosen as a possible culprit in this syndrome; the hypothesis was tested by searching for constitutional p53 mutations in LFS family members.

In our laboratory, Malkin et al. (*12*) studied five families with LFS. DNA from normal tissue was used to detect individuals carrying a mutant p53 gene with the polymerase chain reaction and sequencing of amplified DNA. After DNA was extracted from lymphocytes or fibroblasts, exons 5 through 8 of the p53 gene were amplified and sequenced. In the first and most extensively studied kindred, a mutation at codon 248 of the p53 gene was identified. Three family members with malignancy carried this mutation in constitutional (nontumor) DNA. These included two sisters with breast cancer and a child with a brain tumor. Two carriers of the mutation with no history of malignancy were identified: a 57-year-old male and a 5-year-old female. Three unaffected family members were also identified. In each of the other four families studied, point mutations were found in the p53 gene amplified

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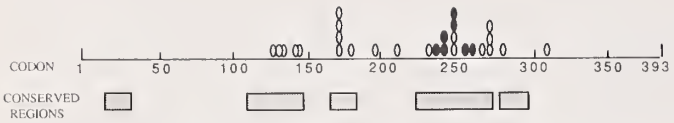


**Figure 1.**—Distribution of human constitutional and tumor p53 point mutations. Map of p53 coding region indicating point mutations noted in human tumor (○) and in constitutional DNA (●). Shaded rectangles signify conserved regions.

from nontumor DNA from family members with malignancies. These mutations occur in the region between codons 245 and 258, a highly conserved region of p53 where mutations in many sporadic tumors have been identified (fig. 1). When Malkin et al. examined DNA from tumor specimens from two affected individuals in two separate families, they found no evidence for presence of the second normal allele, thus supporting a two-hit model.

In independent investigations, Srivastava et al. (*13*) identified an inherited mutation in a germ-line p53 allele in a family with LFS. This mutation was at codon 245 and was seen in the fibroblast DNA from a male patient with both osteosarcoma and a brain tumor, as well as in fibroblast DNA from his brother, father, and two paternal aunts, all with LFS-component tumors.

Although these studies focused on kindreds with LFS, sporadically occurring new germ-line mutations would be expected to occur relatively frequently. In the case of retinoblastoma, for example, although 40% of all patients have constitutional Rb mutations, only 15% of these are inherited (*14*). The remaining 85% are new constitutional mutations presumably acquired during early embyrogenesis. The proportion of cancer patients without LFS with constitutional p53 mutations is unknown. Sheffield et al. (*15*) reported a case in which a child with ependymoma was found to have a constitutional mutation at codon 242. Prosser et al. (*16*) studied five kindreds with familial breast cancer and found no constitutional p53 mutation. There are ongoing studies of additional patient groups investigating the probability that a proportion of patients with seemingly spontaneous malignancies carry constitutional mutations in the p53 gene. Populations that could be studied include infants with cancer, patients with multiple primary cancers or bilateral disease, and women with breast cancer presenting at an early age.

Finally, these findings raise important questions in terms of management of the patient, with or without cancer, who carries a constitutional p53 mutation. These patients are at a high risk of developing malignancy, and studies of the role of medical surveillance, patient education, interactions with environmental mutagens, and the utility of chemoprophylaxis will be performed. The ethical and psychological ramifications will be explored, as well as issues of genetic counseling and prenatal diagnosis. Although constitutional mutations in tumor-suppressor genes are likely to be rare, patients who carry these mutations may help to develop management strategies for patients with other genetic predisposition syndromes.

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# Animal Cancer Tests and Cancer Prevention[1,2]

Bruce N. Ames *and* Lois Swirsky Gold[3,4]

**ABSTRACT—The toxicological significance of exposures to synthetic chemicals is examined in the context of exposures to naturally occurring chemicals. We calculate that 99.99% (by weight) of the pesticides in the US diet are chemicals that plants produce to defend themselves (nature's pesticides). Only 52 of these natural pesticides have been tested in high-dose animal cancer tests, and 27 are rodent carcinogens; these 27 are shown to be present in many common foods. The toxicology of synthetic chemicals is compared to that of natural chemicals, which represent the vast bulk of the chemicals to which humans are exposed. It is argued that animals have a broad array of inducible general defenses to combat the changing array of toxic chemicals in plant food and that these defenses are effective against both natural and synthetic toxins. Synthetic toxins (eg, dioxin) are compared to natural chemicals (eg, indole carbinol [in broccoli] and ethanol). The finding that, in high-dose tests, a high proportion of both natural and synthetic chemicals are carcinogens, mutagens, teratogens, and clastogens (30%–50% for each group) calls into question current efforts to use these tests to protect public health by regulating low doses of synthetic chemicals. The administration of chemicals at the maximum tolerated dose in standard animal cancer tests is postulated to increase cell division (mitogenesis), which in turn increases rates of mutagenesis and, thus, carcinogenesis. The animal data are consistent with this mechanism, because a high proportion—about 50%—of all chemicals tested (whether natural or synthetic) are indeed rodent carcinogens. We conclude that, at the low doses of most human exposures, in which mitogenesis does not occur, the hazards to humans of rodent carcinogens may be much lower than is commonly assumed. [J Natl Cancer Inst Monogr 12:125–132, 1992]**

The great public concern about possible carcinogenic hazards from traces of synthetic chemicals does not take into account the following: 1) An extrapolation from the high doses of animal tests to the low levels of human exposure should be based on an understanding of the mechanisms of carcinogenesis (*1, 2*). 2) The world of natural chemicals makes up the vast bulk of chemicals to which humans are exposed (*3*). 3) The toxicologies of synthetic and natural toxins are not fundamentally different (*4*). 4) About 50% of the natural chemicals tested chronically in rats and mice at the maximum tolerated dose are carcinogens (*1, 3*). 5) Testing at the maximum tolerated dose can frequently cause mitogenesis (a risk factor for cancer that can be limited to the high dose), and ignoring this greatly exaggerates risks (*1*).

Testing chemicals for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess numbers of human cancers that might occur at low-dose exposures (*1, 2*). The attempt to prevent cancer by eliminating low levels of synthetic chemicals by "risk assessment," with worst-case one-in-a-million risk scenarios based on rodent tests, is not scientifically justified.

## MECHANISMS OF CARCINOGENESIS

Geneticists have long known that cell division is critical for mutagenesis. If mutagenesis is considered important for carcinogenesis, it follows that mitogenesis must be important (fig. 1). The inactivation of tumor-suppressor genes is also known to be important in carcinogenesis, and evidence suggests that one of the functions of tumor-suppressor genes is to inhibit mitogenesis (*5*). Once the first copy of a tumor-suppressor gene is mutated, the inactivation of the second copy (loss of heterozygosity) is more likely to be caused by processes whose frequency is dependent on cell division (mitotic recombination, gene conversion, and nondisjunction) than by an independent second mutation (*1, 2*). Therefore, loss of heterozygosity will be stimulated by increased mitogenesis. Thus, although the stimulation of mitogenesis increases the chance of every mutational step, it is a much more important factor for tumor induction after the first mutation has occurred. This explains why mutagenesis and mitogenesis are synergistic (*1, 2*) and why mitogenesis after the first mutation is more effective than before. Naming this *initiation* and *promotion* does not clarify any mechanistic issues (*6*). The idea that "promoters" are not in themselves carcinogens is not credible on mechanistic grounds and is not correct on experimental grounds (*1, 2, 6*): every classic promoter that has been tested adequately [eg, phenobarbital, catechol, and 12-O-tetradecanoyl phorbol-

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[2]This article was adapted in part from (*1–5*) and Ames BN, Gold LS, in the Princess Takamatsu Cancer Research Fund Symposium (*57*), which presents the arguments in more detail.

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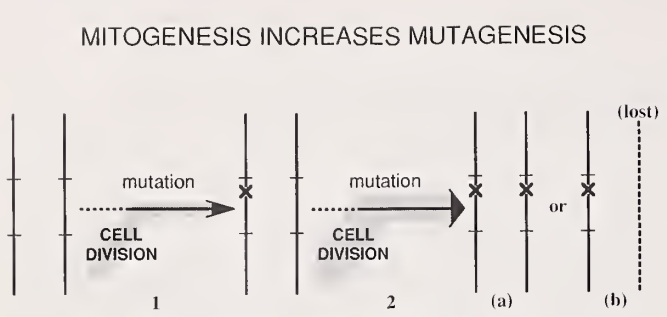


**Figure 1.**—Mitogenesis (induced cell division) is major multiplier of endogenous (or exogenous) DNA damage leading to mutation. Pathway to inactivating (X) both copies of recessive tumor-suppressor gene is shown (two *vertical lines* represent pair of chromosomes carrying genes). Cell division increases mutagenesis due to following: DNA adducts converted to mutations before they are repaired (1 and 2a), mutations due to DNA replication (1 and 2a), and vulnerability of replicating DNA to damage (1 and 2a). Mitotic recombination (2a), gene conversion (2a), and nondisjunction (2b) are more frequent, and first two give rise to same mutation on both chromosomes. Diagram does not attempt to deal with complex mutational pathway to tumors.

13-acetate (TPA)] is a carcinogen. The word *promoter* alone confuses the issue, because mitogenesis may be caused by one dose of a chemical and not by a lower dose. Dominant oncogenes and their clonal expansion by mitogenesis can clearly be involved in carcinogenesis, adding complexity; however, these mechanisms are still consistent with the view that mitogenesis is an important factor in carcinogenesis.

Chronic mitogenesis by itself can be a risk factor for cancer: Theory predicts it and a large body of literature supports it (*1, 7*). Mitogenesis can often be the dominant factor in chemical carcinogenesis at high doses, ie, close to the maximum tolerated dose (MTD). Mitogenesis can be caused by toxicity of chemicals at high dose (cell killing and subsequent replacement), by interference with cell-cell communication at high doses (*8–11*) by substances such as hormones binding to receptors that control cell division (*7*), by oxidants (the wound-healing response), by viruses, and by other agents (*1*). The important factor is not toxicity but increased mitogenesis in those cells that are not discarded.

Nongenotoxic agents (eg, saccharin) can be carcinogens at high doses just by causing cell killing with chronic mitogenesis and inflammation, and the dose response would be expected to show a threshold (*1, 12, 13*). Genotoxic chemicals, because they hit DNA, are even more effective than nongenotoxic chemicals at causing cell killing and cell replacement at high doses. Because genotoxic chemicals also act as mutagens, they can produce a multiplicative interaction not found at low doses, leading to an upward-curving dose response for carcinogenicity (*1, 12, 13*). Because the effects of mitogenesis usually occur only at high doses, this should be factored into risk assessment. The 40% of rodent carcinogens that are not detectable mutagens should be investigated to see if their carcinogenic effects result from inducing mitogenesis and therefore are unlikely to be a risk at low doses. If the National Toxicology Program cancer bioassay included measurements of mitogenesis, then regulators could factor the effects of mitogenesis into risk assessment rather than rely on linear extrapolation.

Epigenetic factors are also involved in carcinogenesis. However, both mitogenesis (through mitotic recombination) and DNA damage can cause loss of 5-methylC or other epigenetic modification (*1*).

Mutagens are often thought to be only exogenous agents, but endogenous mutagens cause massive DNA damage (by formation of oxidative and other adducts) that can be converted to stable mutations during cell division. We have estimated that a normal rat cell has on average about $10^6$ oxidative adducts at any one time and that this number increases with age (*14, 15*). Also, about $10^5$ new oxidative adducts per cell are formed every day, and most are repaired (*14, 15*). These are the same adducts produced by radiation, an oxidative mutagen. Our conclusion is that this endogenous oxidative damage is a major factor in both aging and the degenerative diseases of aging such as cancer. This high endogenous level of oxidative adducts reinforces evidence from epidemiology that both deficiency of antioxidants (*16*) and mitogenesis (*1, 7*) are likely to be important risk factors for cancer.

## Causes of Human Cancer

Henderson et al. (*7, 17*) and others (*1*) have discussed the importance of chronic mitogenesis for many, if not most, of the known causes of human cancer, eg, hormones in breast cancer; hepatitis B (*18*) or C viruses or alcohol in liver cancer; high salt or *Helicobacter (Campylobacter)* infection in stomach cancer; papilloma virus in cervical cancer; asbestos or tobacco smoke in lung cancer; and excess animal fat and low calcium in colon cancer. For chemical carcinogens associated with occupational cancer, worker exposure has been primarily at high, near-toxic doses that might be expected to induce mitogenesis. Permitted worker exposure levels for some rodent carcinogens are too close to the doses that induce tumors in test animals (*19*). For high occupational exposures, little extrapolation is required from the doses used in rodent bioassays; therefore, assumptions about extrapolation are less important.

Epidemiologists are frequently discovering clues about the causes of human cancer, and the resulting hypotheses are then refined by animal and metabolic studies. During the next decade, it appears likely that this approach will lead to an understanding of the causes of the major human cancers. Current epidemiological data point to several risk factors for human cancer: cigarette smoking (which is responsible for 30% of cancer deaths), dietary imbalances, infections, hormones, and occupation. "The age adjusted mortality rate for all cancers combined except lung cancer has been declining since 1950 for all individual age groups except 85 and above" (*20*). Although incidence rates for some cancers have been rising, trends in recorded incidence rates may be biased by improved registration and diagnosis. Even though mortality rates for cancers at particular sites can be shown to be

increasing (eg, non-Hodgkin's lymphoma and melanoma) or decreasing (eg, stomach, cervical, and rectal), establishing causes remains difficult because of the many changing aspects of our life-style. Life expectancy continues to increase every year.

Cancer clusters in small areas are expected to be common by chance alone, and epidemiology lacks the power to establish causality in these cases (*21*). It is important to show that a pollution exposure that purportedly causes a cancer cluster is significantly greater than the background of exposures to naturally occurring rodent carcinogens.

### Causes of Cancer in Animal Tests

Animal cancer tests are conducted at the MTD of the test chemical for long periods, which can cause chronic mitogenesis (*1, 12, 22*). Chronic dosing at the MTD can be thought of as chronic wounding, which is known to be both a promoter of carcinogenesis in animals and a risk factor for cancer in humans. Thus, a high percentage of all chemicals might be expected to be carcinogenic at chronic, near-toxic doses, and this is exactly what is found. About half of all chemicals tested chronically at the MTD are carcinogens (*1, 3*).

Synthetic chemicals account for 82% (350 of 427) of the chemicals that have been adequately tested in both rats and mice (*1*). Despite the fact that humans eat vastly more natural than synthetic chemicals, the world of natural chemicals has never been tested systematically (*3*). Of the natural chemicals tested, approximately half are carcinogens, which is approximately the same as has been found for synthetic chemicals (*1, 3*). It is unlikely that the high proportion of carcinogens in rodent studies is due simply to selection of suspicious chemical structures: Most chemicals were selected because of their use as industrial compounds, pesticides, drugs, or food additives. Moreover, knowledge to predict carcinogenicity historically has been inadequate.

## NATURE'S PESTICIDES

"Plants are not just food for animals. . .The world is not green. It is colored lectin, tannin, cyanide, caffeine, aflatoxin, and canavanine" (*23*).

### Dietary Pesticides Are 99.99% Natural

Nature's pesticides are one important subset of natural chemicals (*3*). Plants produce toxins to protect themselves against fungi, insects, and animal predators. Tens of thousands of these natural pesticides have been discovered, and every species of plant analyzed contains its own set of perhaps a few dozen toxins. When plants are stressed or damaged, such as during a pest attack, they may greatly increase their natural pesticide levels, occasionally to levels that can be acutely toxic to humans. We estimate that Americans eat about 1.5 g of natural pesticides per person per day, which is about 10 000 times more than they eat of synthetic pesticide residues.

Concentrations of natural pesticides in plants are usually measured in parts per thousand or million rather than parts per billion, the usual concentration of synthetic pesticide residues or of water pollutants (*1*). We estimate that humans ingest roughly 5000–10 000 different natural pesticides and their breakdown products (*1*). For example, 49 natural pesticides (and metabolites) are ingested when cabbage is eaten: Only two have been tested for carcinogenicity (*1*). Lima beans contain a completely different array of 23 natural toxins that, in stressed plants, range in concentration from 0.2 to 33 parts per thousand fresh weight; none appears to have been tested yet for carcinogenicity or teratogenicity (*24*). Many Leguminosae contain canavanine, a toxic arginine analogue that, after being eaten by animals, is incorporated in protein in place of arginine. Feeding alfalfa sprouts (1.5% canavanine dry weight) or canavanine to monkeys causes a lupus erythematosus–like syndrome (*25*). Lupus in humans is characterized by a defect in the immune system that is associated with autoimmunity, antinuclear antibodies, chromosome breaks, and various types of pathology. The toxicity of nonfood plants is well known: Plants are among the most commonly ingested poisonous substances for children under 5 years of age.

Surprisingly few plant toxins have been tested for carcinogenicity (*3*). Among 1052 chemicals tested in at least one species in chronic cancer tests, only 52 are naturally occurring plant pesticides (*3*). Among these, about half (27 of 52) are carcinogenic. Even though only a tiny proportion of the plant toxins in the human diet has been tested so far, the 27 natural pesticides that are rodent carcinogens are present in the following foods (those at levels >10 ppm are in italics): *anise, apple,* apricot, banana, *basil,* broccoli, *Brussels sprouts, cabbage,* cantaloupe, *caraway, carrot, cauliflower, celery, cherries,* cinnamon, cloves, cocoa, *coffee* (brewed), collard greens, *comfrey herb tea*, currants, *dill, eggplant, endive, fennel, grapefruit juice, grapes,* guava, *honey,* honeydew melon, *horseradish,* kale, lentils, *lettuce, mango, mushrooms, mustard* (brown), *nutmeg, orange juice, parsley, parsnip,* peach, *pear,* peas, *pepper* (black), pineapple, *plum, potato,* radish, raspberries, *rosemary, sage, sesame seeds* (heated), *tarragon,* tea, *thyme,* tomato, and turnip. Thus, almost every fruit and vegetable on the market probably contains natural plant pesticides that are rodent carcinogens. The levels of these 27 rodent carcinogens in the plants above are commonly thousands of times higher than the levels of synthetic pesticides.

Caution is necessary in interpreting the implications of ingesting natural pesticides that are rodent carcinogens. It is not argued here that these dietary exposures are necessarily of much relevance to human cancer. What is important in our analysis is that exposures to natural rodent carcinogens and the high proportion of those that are carcinogenic casts doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens. Particular natural pesticides that are carcinogenic in rodents can be bred out of crops if studies of mechanisms indicate that they may be significant hazards to humans.

### Residues of Synthetic Pesticides

The US Food and Drug Administration (FDA) has assayed food for 200 chemicals, including the synthetic pesticide residues thought to be of greatest importance and the residues of some industrial chemicals such as polychlorinated biphenyls (*26*). The FDA found residues for 105 of these chemicals: The US intake of the sum of these 105 chemicals averages about 0.09 mg/person/d, which we compare to 1.5 g of natural pesticides (ie, 99.99% natural). Other analyses of synthetic pesticide residues are similar (*27*). About half (0.04 mg) of this daily intake of synthetic pesticides is composed of four chemicals that were not carcinogenic in rodent tests: ethylhexyl diphenyl phosphate, chlorpropham, malathion, and dicloran (*26*). Thus, the intake of known or potential rodent carcinogens from synthetic residues is only about 0.05 mg/d (averaging ~60 ppb in plant food).

### Cooking Food

The cooking of food is also a major dietary source of potential rodent carcinogens. Cooking produces about 2 g/person/d of mostly untested burnt material that contains many rodent carcinogens—eg, polycyclic hydrocarbons, heterocyclic amines (*28, 29*), furfural, nitrosamines, and nitroaromatics—as well as a plethora of mutagens (*28, 30*). Thus, the number and amounts of carcinogenic (or total) synthetic pesticide residues appear to be minimal compared with the background of naturally occurring chemicals in the diet. Roasted coffee, for example, is known to contain 826 volatile chemicals, of which 21 have been tested chronically and 16 are rodent carcinogens; caffeic acid, a nonvolatile rodent carcinogen, is also present (*3*). A typical cup of coffee contains at least 10 mg (40 ppm) of rodent carcinogens (mostly caffeic acid, catechol, furfural, hydroquinone, and hydrogen peroxide) (*3*), about equivalent in weight to the potentially carcinogenic synthetic pesticide residues an American eats in a year (assuming half of the untested synthetic residue weight will be carcinogenic in rodents) (*1*).

The evidence on coffee and human health has recently been reviewed, and the evidence to date is insufficient to show that coffee is a risk factor for cancer in humans (*16*). The same caution discussed above about the implications for humans of natural rodent carcinogens in the diet applies to coffee and the products of cooked food.

A broader view of the chemical world must be taken and attempts made to identify the greatest potential natural or synthetic carcinogenic hazards; only a tiny fraction of the chemicals humans are exposed to are ever going to be tested in rodent bioassays. We recently compared the possible hazards of some rodent carcinogens, using the human exposure:rodent potency (HERP) ratio (*31*) and permitted exposure:rodent potency (PERP) ratio (*19*). The HERP ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, although whether these natural exposures are likely to be of major or minor importance is unknown. The PERP ranking suggests that some permitted occupational exposures rank very high.

One strategy for choosing chemicals to test is to prioritize chemicals according to how they might rank in possible hazard if they were to be identified as rodent carcinogens. A useful first approximation is the analogous ratio of human exposure to rodent toxicity (HERT). HERT would use readily available $LD_{50}$ (lethal dose) values rather than the $TD_{50}$ (carcinogenic potency) values used in HERP. $LD_{50}$ is related to the MTD and the $TD_{50}$ (*22, 32, 33*), and the ranking of human exposures on HERP and HERT will be similar (Gold LS: unpublished observations). The number of people exposed is also relevant in attempting to prioritize systematically among chemicals. Chemicals with high HERT and population exposure could then be investigated in more detail as to mutagenicity, mitogenicity, pharmacokinetics, and so forth. Natural and synthetic chemicals could both be ranked, and if natural chemicals in foods (eg, chlorogenic acid in coffee, psoralens in celery, or indole carbinol in broccoli) turned out to be important, they might be bred out or, for processed foods such as coffee, extracted.

### Dioxin

Cabbage and broccoli contain a chemical whose breakdown products bind to the body's Ah receptor, induce the defense enzymes under the control of the receptors, and possibly cause mitogenesis—as does dioxin [2,3,7,8–tetrachlorodibenzo-*p*-dioxin (TCDD)], one of the most feared industrial contaminants. TCDD is of great public concern because it is carcinogenic and teratogenic in rodents at extremely low doses. The doses humans ingest are, however, far lower than the lowest doses that have been shown to cause cancer and reproductive damage in rodents.

TCDD exerts many or all of its harmful effects in mammalian cells through binding to the Ah receptor (*34*). Many natural substances also bind to the Ah receptor (eg, tryptophan oxidation products [*35*]), and insofar as they have been examined, they have similar properties to TCDD. A cooked steak, for example, contains polycyclic hydrocarbons that bind to the Ah receptor and mimic TCDD. In addition, various flavones and other plant substances in the diet, such as indole carbinol (IC), also bind to the Ah receptor. IC is the main breakdown compound of glucobrassicin, a glucosinolate that is present in large amounts in vegetables of the *Brassica* genus, including broccoli (25 mg/100-g portion), Brussels sprouts (125 mg/100 g), and cabbage (25 mg/100 g) (*36, 37*). When tissues of these vegetables are lacerated, as occurs during chewing, they release an enzyme that breaks down the glucobrassicin. The enzyme is heat stable, and cooked vegetables yield most of the indole compounds in raw vegetables (*38*). Therefore, we assume for the following calculation that 20% of glucobrassicin is converted to IC on eating. At the pH of the stomach, IC makes dimers and trimers that induce the same set of detoxifying enzymes as TCDD (*38–40*). IC, like TCDD, protects against carcinogenesis when given before aflatoxin or other car-

cinogens (*40–42*). However, when given after aflatoxin or other carcinogens, IC, like TCDD, stimulates carcinogenesis (*42*). This stimulation of carcinogenesis has also been shown for cabbage itself.

These IC dimers and trimers appear to be much more of a potential hazard than TCDD, assuming that binding to the Ah receptor is critical for toxic effect. The Environmental Protection Agency's (EPA) human reference dose (formerly *acceptable dose limit*) of TCDD is 6 $fg/kg^{-1}/d^{-1}$. This should be compared with 5 mg IC/100 g of broccoli or cabbage (*3*). Although the affinity of one major indole dimer in binding to Ah receptors is less than that of TCDD by a factor of about 8000 (Bjeldanes LF and Bradfield CA: unpublished observations), the effective dose to the Ah receptor from a helping of broccoli would be about 1500 times higher than that of TCDD, taking into account an extra factor of 1000 for the long lifetime of TCDD in the body (several years) and assuming that the lifetime of the hydrophobic indole dimers is as short as 1 day. Another IC dimer has recently been shown to bind to the Ah receptor with about the same affinity as TCDD (Bjeldanes LF: unpublished observations). However, it is not clear whether, at the low doses of human exposure, either IC or TCDD is hazardous; they may even be protective. It seems likely that many more of these natural "dioxin simulators" will be discovered in the future.

TCDD seems of minor interest as a teratogen or carcinogen compared with ethanol. Alcoholic beverages are the most important known human chemical teratogen (*16*). In contrast, there is no persuasive evidence that TCDD is either carcinogenic or teratogenic in humans, although it is both at near-toxic doses in rodents. If the teratogenic potential of TCDD is compared to that of alcohol (after adjusting for their respective teratogenic potencies as determined in rodent tests), then daily consumption of the EPA's reference dose of TCDD (6 fg/kg) would be equivalent in teratogenic potential to a daily consumption of alcohol from 1/3 000 000th of a beer. That is equivalent to drinking a single beer (15 g ethyl alcohol) over 8000 years.

Alcoholic beverages in humans are a risk factor for cancer and birth defects. A comparison of the carcinogenic potential for rodents of TCDD with that of alcohol (adjusting for the potency in rodents) shows that ingesting the TCDD reference dose of 6 $fg/kg^{-1}/d^{-1}$ is equivalent to ingesting one beer every 345 years (*4*). Because the average consumption of alcohol in the United States is equivalent to more than one beer per person per day, and because five drinks a day are a carcinogenic risk in humans, the experimental evidence does not of itself seem to justify the great concern over TCDD at levels in the range of the reference dose.

## SIMILARITY OF TOXICOLOGY OF SYNTHETIC AND NATURAL TOXINS

It is often assumed that, because plants are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms that animals have evolved to cope with the toxicity of natural chemicals will fail to protect humans against synthetic chemicals. For example, Rachel Carson (*43*) stated, "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death." We find this assumption flawed for several reasons.

Defenses that animals have evolved are mostly of a general type, as might be expected, because the number of natural chemicals that might have toxic effects is so large (*4*). General defenses offer protection not only against natural but also against synthetic chemicals, making humans well buffered against toxins (*4*). These defenses include the following: 1) The continuous shedding of cells exposed to toxins (the surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days). 2) The induction of various general detoxifying mechanisms, such as antioxidant defenses or the phase II electrophile-detoxifying systems (eg, glutathione transferases): cells that are exposed to small doses of an oxidant, eg, radiation or hydrogen peroxide, induce antioxidant defenses and become more resistant to higher doses, whether the oxidant is synthetic or natural—natural or synthetic electrophiles induce phase II detoxifying enzymes that are effective against both. 3) Planar hydrophobic molecules (natural or synthetic) are actively excreted from liver and intestinal cells. 4) DNA repair is effective against DNA adducts formed from both synthetic and natural chemicals and is inducible in response to DNA damage.

Anticarcinogenic chemicals in the diet (eg, antioxidants) help to protect humans against carcinogens but do not distinguish between synthetic and natural carcinogens. It has been argued that synergism between synthetic carcinogens could multiply hazards, but this is equally true of natural carcinogens.

The fact that defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses against toxins is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new foods when favored foods became scarce or evolved new toxins.

Various natural toxins, some of which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates. Mold aflatoxins, for example, have been shown to cause cancer in trout, rats, mice, monkeys, and, possibly, humans. Eleven mold toxins of 16 tested have been reported to be carcinogenic (*3*). Many of the common elements are carcinogenic (eg, salts of lead, cadmium, beryllium, nickel, chromium, selenium, and arsenic) or clastogenic at high doses, despite their presence throughout evolution (*3, 4*). Selenium and chromium are essential trace elements in animal nutrition.

Humans have not had time to evolve into a "toxic harmony" with all of the plants in their diet. Indeed, few

of the plants that modern humans eat would have been present in an ancestral African hunter-gatherer's diet. The human diet has changed drastically in the last few thousand years, and most humans are eating many recently introduced plants that their ancestors did not (eg, coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives, and kiwifruit). In addition, cruciferous vegetables (eg, cabbage, broccoli, kale, cauliflower, and mustard) were used in ancient times "primarily for medicinal purposes" and were used as foods across Europe only in the Middle Ages (*3, 4*). Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants.

DDT bioconcentrates in the food chain due to its unusual lipophilicity; however, natural toxins can also bioconcentrate. DDT is often viewed as the typically dangerous synthetic pesticide because it persists for years; it was representative of a class of chlorinated pesticides. Natural pesticides, however, also bioconcentrate if lipophilic: For example, the teratogens from potato, solanine (and its aglycon solanidine), and chaconine are found in the tissues of potato eaters (*44–46*). Although DDT was unusual with respect to bioconcentration, it was remarkably nontoxic to mammals, saved millions of lives, and has not been shown to cause harm to humans (*47*). To a large extent, DDT, the first major synthetic insecticide, replaced lead arsenate, a major pesticide used before the modern era. Lead arsenate is even more persistent than DDT, and, although natural, both lead and arsenic are carcinogenic. When the undesirable bioconcentration and persistence of DDT and its lethal effects on some birds were recognized, it was prudently phased out, and less persistent chemicals were developed to replace it. Examples are the synthetic pyrethroids that disrupt the same sodium channel in insects as DDT, are degraded rapidly in the environment, and can often be used at a concentration as low as a few grams per acre.

Positive results are remarkably common in high-dose screening tests for carcinogens, clastogens (agents that break chromosomes), teratogens, and mutagens. About half of the chemicals tested, whether natural or synthetic, are carcinogens in chronic, high-dose rodent tests (*1, 3*), and about half are clastogens in tissue culture tests (*48*). A high proportion of positives is also reported for rodent teratogenicity tests: 38% of the 2800 chemicals tested in laboratory animals "have been teratogenic" in the standard, high-dose protocol (*49*). It is therefore reasonable to assume that a sizable percentage of both synthetic and natural chemicals will be reproductive toxins at high doses. Mutagens may also be common: Of 340 chemicals tested for carcinogenicity in both rats and mice and for mutagenicity in *Salmonella*, 46% were mutagens, and mutagens were nearly twice as likely to be carcinogenic than were nonmutagens (*50*; Gold LS: unpublished observations). Of these 340 chemicals, 70% were either mutagens or carcinogens or both. How much this high frequency of positive results is due to bias in selecting chemicals is not known. Even if selection bias doubled the percentage of positives, which we think is unlikely, the high proportion of positives would still mean that almost everything natural that humans eat contains carcinogens, mutagens, teratogens, and clastogens. Thus, testing a random group of natural pesticides and pyrolysis products from cooking should be a high priority so an adequate comparison to synthetic toxins can be made.

These arguments undermine many assumptions of current regulatory policy and necessitate a rethinking of policy designed to reduce human cancer. Minimizing pollution is a separate issue and is clearly desirable for reasons other than effects on public health. There is much literature on why focusing on worst-case one-in-a-million risks rather than major risks "impedes intelligent risk reduction" (*51*). For example, synthetic pesticides have markedly lowered the cost of plant food, thus increasing consumption. Eating more fruits and vegetables and less fat appears to be the best way to lower risks of cancer and heart disease, other than giving up smoking.

It is by no means clear that many significant risk factors for human cancer will be discovered by screening assays. Dietary imbalances, such as antioxidant (*16, 52*) and folate (*53*) deficiencies, are likely to be major contributors to human cancer, and understanding these should be, but is not, a major priority of research. Understanding why calorie restriction dramatically lowers mitogenesis rates and cancer rates and extends life span in experimental animals (*54–56*) should be a major research priority. More studies on mechanisms of carcinogenesis should also be of high priority.

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# Leukemia in Children and Paternal Radiation Exposure at the Sellafield Nuclear Site

Martin J. Gardner[1]

**ABSTRACT—Childhood cancer around nuclear installations has been studied in recent years, particularly in the United Kingdom but also in other countries. The early studies were prompted by the suggestion of a 10-fold raised level of childhood leukemia around the Sellafield nuclear site in England, which was confirmed and followed by the identification of generally smaller excesses around some (but not all) other nuclear sites in the United Kingdom. Marked excesses have not been reported in other countries. The increased leukemia rate around Sellafield has been further investigated by examining individual cases in detail in epidemiological cohort and case-control studies. The raised incidence seems to have been concentrated in children born in the local area but not among children who moved in after birth and was particularly associated with fathers who had experienced higher levels of occupational external ionizing radiation exposure at Sellafield before their children's conception. The underlying cause of this statistical association is not yet clear, but the findings have important potential implications for radiobiology and for protection of radiation workers and their children. [J Natl Cancer Inst Monogr 12:133–135, 1992]**

The Sellafield site is located in northwest England on the coast of West Cumbria. The site was acquired in 1947 for the production of plutonium for defense purposes, with two nuclear reactors and a spent-fuel reprocessing plant being in operation by 1952. These reactors and the reprocessing plant were subsequently closed and replaced between 1956 and 1963 with five additional nuclear reactors (one of which was closed in 1981); in 1964, the reprocessing plant was replaced. The Sellafield plant reprocesses spent fuel from nuclear power stations in the United Kingdom and abroad and has both stored and discharged to sea low-level radioactive waste—solid and liquid waste, respectively.

A 1983 television documentary suggested that the rate of childhood leukemia was high in the locality of the Sellafield site and alleged that these high rates were linked to the environmental discharges of radiation from the plant. A committee of inquiry into the allegations reported in 1984 (*1*), and three features are relevant here. First, geographic analyses of routinely collected cancer registration and mortality data on children enabled the committee to conclude that leukemia rates in the vicinity of Sellafield were indeed high, if not totally extreme, in the regional and national picture. Second, analyses using models of the average radiation dose to the bone marrow received as a consequence of the radioactive discharges from Sellafield did not support the view that an environmental pathway was involved. Third, the report recommended carrying out detailed epidemiological studies in an attempt to explore further the childhood leukemia excess and any potential explanations.

## EPIDEMIOLOGICAL STUDIES

### Cohort Studies

The village of Seascale, which is about 3 km south of the Sellafield site, had been particularly implicated as having a raised level of childhood leukemia. Thus, it was decided to study all children who at some stage of their lives had resided in the village, particularly to overcome some of the disadvantages of geographic analyses and to include observations on children after they had moved away from Seascale. These cohort studies included, as far as possible, all children born since 1950 who at some age lived in Seascale (*2, 3*). Their names and other particulars were identified from birth and school registers, and the cohorts comprised 1068 children born in Seascale and a further 1546 children who attended schools in Seascale after having been born elsewhere. Records of mortality and cancer registration on these children were obtained, and the findings confirmed the geographic analyses of a raised level of leukemia among Seascale children. However, the excess appeared to be concentrated among children born in Seascale in contrast to those moving in after birth to attend one of the local schools (table 1). Thus, there was a 10-fold excess of leukemia and a 2-fold excess of other cancers among the births, with no increased rates among the schoolchildren who moved to Seascale after birth. The differential findings in the birth and school cohorts suggested that one or more factors might have acted on a locality-specific basis before birth or early in life to produce the increased childhood leukemia rate.

### Case-Control Study

A case-control study has been carried out including all cases of leukemia and lymphoma diagnosed at less than 25

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**Table 1.**—Leukemia and other cancer cases during 1950–1986 in Seascale birth and school cohorts

| Diagnosis cohort | No. of cases: Observed (O) | No. of cases: Expected (E)* | O/E | 95% Confidence interval for O/E |
|---|---|---|---|---|
| Leukemia | | | | |
| Birth | 6† | 0.6 | 10.0 | 3.7–21.8 |
| Schools | 0 | 0.6 | 0 | 0–6.2 |
| Other cancers | | | | |
| Birth | 6 | 2.2 | 2.7 | 1.0–5.9 |
| Schools | 4 | 3.4 | 1.2 | 0.3–3.0 |

*At age, sex, and calendar-period–specific rates for England and Wales.

†Five cases of leukemia were diagnosed while resident in Seascale and are included in the case-control study (*see* fig. 1).

years of age in the West Cumbria area between 1950 and 1985 (*4, 5*). This area was chosen to include coastal and inland areas where concern had been raised about potential risks from radiation contamination due to discharges to sea and air from the nuclear plant and to cover the places of residence of the Sellafield work force.

The aim was to obtain information on individual cases and control subjects that might help to explain the excesses found in the geographic and cohort studies. Factors examined included prenatal x-ray exposure as the only generally accepted cause for childhood leukemia, various suspected risk factors (eg, viral illnesses, social class, and maternal age), behavioral habits (eg, eating fresh seafood and playing on the beach, which might have enhanced exposure to radionuclides released from Sellafield), and parental occupation and radiation exposure at Sellafield. The control children for the study were taken from the same birth registers into which the case subjects' births were entered. For each case subject, two sets of eight control subjects were taken of the same sex and adjacent in date of birth, with one set covering the total birth registration area (area control subjects) and the other set confined to the same local village where the case subject was born (local control subjects).

The identifying details on the parents of the case and control subjects were cross-linked with the past and present Sellafield work-force file; when matches were found, individual records of external ionizing radiation exposure were obtained from British Nuclear Fuels. It was in this respect that the most important result was identified, although the expected geographic distribution of leukemia and association with prenatal x rays were also found (*4*).

The relationship between preconceptual radiation dose of the fathers during their employment and leukemia in their children is shown in table 2 for local control subjects. High relative risks are found for paternal exposures over 100 milliSieverts (mSv) accumulated over their total preconceptual employment period and over 10 mSv during the 6 months before their children's conception, albeit based on small numbers. Three of the four cases in the upper ranges were born in Seascale. Of the remaining three Seascale cases of leukemia shown in table 1, the father of one had an accumulated preconceptual radiation dose of 96 mSv, and the father of another has not yet been linked to the Sellafield work-force file; the third case was diagnosed after leaving West Cumbria and was therefore excluded from this case-control study. The findings in relation to local control subjects for Seascale case children are shown in figure 1, in which it can be seen that each of the four linked case fathers had higher radiation doses than all the matched control fathers. Comparable results were found for area control subjects. Data from questionnaires to parents did not suggest any relationship of childhood leukemia to potential sources of enhanced exposure to radionuclides discharged to sea from the nuclear site. Similar results in relation to father's employment at Sellafield were found for non-Hodgkin's lymphoma, although the number of cases was smaller, but not for Hodgkin's disease. The contrast is interesting because Hodgkin's disease is not thought of as a radiation-related condition.

**Table 2.**—Relative risks for childhood leukemia by father's external ionizing radiation dose during employment at Sellafield before child's conception

| Radiation dose, mSv | No. of cases | Local control subjects | Odds ratio | 95% Confidence interval |
|---|---|---|---|---|
| *Total before conception* | | | | |
| 0 | 38 | 236 | 1.0 | |
| >0–49 | 3 | 26 | 0.8 | 0.2–3.0 |
| 50–99 | 1 | 11 | 0.8 | 0.1–7.7 |
| ≥100 | 4 | 3 | 8.4 | 1.4–52.0 |
| *Six months before conception* | | | | |
| 0 | 38 | 246 | 1.0 | |
| >0–4 | 3 | 24 | 1.1 | 0.3–4.9 |
| 5–9 | 1 | 3 | 3.0 | 0.3–32.6 |
| ≥10 | 4 | 3 | 8.2 | 1.6–41.7 |

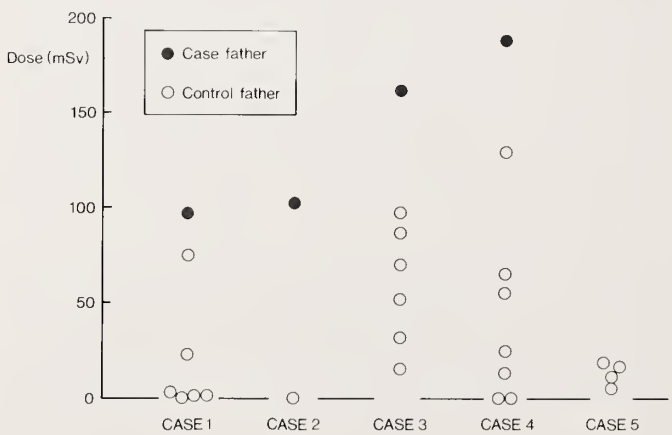


**Figure 1.**—Accumulated external ionizing radiation dose during employment at Sellafield before children's conception in fathers of Seascale leukemia case subjects and Seascale control subjects (the father of case 5 has not yet been linked to radiation dosimetry records).

## DISCUSSION

The association of childhood leukemia with the father's dose of radiation during employment at Sellafield is sufficiently strong to explain statistically the excess incidence rate in Seascale, but the interpretation in terms of a related causal mechanism, if there is one, is not known. Although there is one animal laboratory study that suggests a pathway involving radiation of the father (*6*), the examination of radionuclides and other occupational exposures is under way. In the meantime, radiation exposure of workers at Sellafield has been declining from the peak levels of the 1950s, and no cases of children with leukemia born since 1975 in Seascale are currently known. Further potential preventive measures, such as trials of personal dosimeters that emit an audible signal at a given raised dose rate, together with educational diagrams and leaflets, are being used.

In other countries, geographic analyses have not consistently found raised levels of childhood leukemia in the vicinity of nuclear installations as in the United Kingdom. However, the geographic areas used have sometimes been too large for a localized effect to be shown. Consideration is now being given to case-control studies, such as described in this article, being carried out in the United States and France. Two other studies are currently under way in the United Kingdom.

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# Relationship of Hormone Use to Cancer Risk[1]

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**ABSTRACT—Exogenous hormones are widely prescribed in the United States, primarily as oral contraceptives and hormone-replacement therapy. Each of these frequently used categories of drugs has important potential for altering risk of several major human cancers. The efficacy of oral contraceptives in preventing ovarian cancer and endometrial cancer is well established. There remains controversy about the relationship between oral-contraceptive use and breast cancer risk, but most studies show that use in the postmenarcheal and perimenopausal periods is associated with an increased risk of breast cancer in a duration-dependent manner. As with oral contraceptives, the relationship between estrogen-replacement therapy and breast cancer risk is controversial, but several well-designed studies showed a moderate increased risk after long-term use. Estrogen-replacement therapy is a major cause of endometrial cancer. Combination hormone-replacement therapy will probably reduce some of the excess risk of endometrial cancer, but few epidemiological data exist on this relationship. The sparse data suggest that combination therapy may enhance breast cancer risk. As with endometrial and ovarian cancers, hormonal chemoprevention of breast cancer is also feasible. We review two such strategies, ie, gonadotropin-releasing hormone agonists and the antiestrogenic drug tamoxifen. [J Natl Cancer Inst Monogr 12:137–147, 1992]**

Neoplasia of tissues that are responsive to hormones accounts for more than 20% of all newly diagnosed male and more than 40% of all newly diagnosed female cancers in the United States. Because of the evidence that endogenous hormones affect the risk of these cancers (*1*, *2*) and the importance of these cancers in absolute frequency, reason for concern exists about the effects on cancer risk if the same or closely related hormones are administered for therapeutic purposes, eg, as contraceptives or as hormone-replacement therapy (HRT). We summarize the vast amount of epidemiological information regarding the effects of therapeutic hormones on the risk of cancer.

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## ORAL CONTRACEPTIVES

Because of the widespread use of oral contraceptives (OCs) for birth control, the assessment of the possible relationship between OC use and cancer continues to be of great importance to public health. The body of literature on the relationship between OC use and cancers of the endometrium, ovary, breast, and cervix is substantial. There have also been reports of a relationship between OC use and liver cancer.

### Endometrial Cancer

While the association of prolonged use of estrogen-replacement therapy (ERT) and endometrial cancer was being established, case-series reports suggested a similar association between sequential OCs and endometrial cancer (*3*). That sequential OCs had this effect on the endometrium is not surprising, because these formulations result in a menstrual cycle that begins with a 14- to 16-day proliferation phase (unopposed estrogen), followed by a short, 7-day secretory phase (estrogen-progestogen combination), and ending with a 5- to 7-day period with low unopposed estrogen. Three case-control studies with sufficient data on the use of sequential OCs showed a two-fold increased risk with use of these preparations (*4–6*).

In contrast to the adverse effects on the endometrium of sequential OCs, use of combination OCs has consistently been reported in case-control studies to decrease the risk of endometrial cancer by about 50% (*4–11*). Prospective cohort studies demonstrated similar decreases in risk (*12*, *13*). A protective effect of combination OCs is biologically plausible because the administration of a progestogen with an estrogen greatly reduces endometrial mitotic activity.

In the large Cancer and Steroid Hormone (CASH) Study sponsored by the Centers for Disease Control and the National Institute of Child Health and Human Development, no apparent difference in risk appeared for short-term use of combination OCs (<5 years) compared with longer use (*4*), although very short term users (<1 year) were not protected (*10*). In contrast, Henderson et al. (*5*) observed a clear decrease in risk with longer use. For 6 years or more of use, the relative risk was 0.14 compared with lifetime nonuse.

Whether the protective effect persists with increasing time since last use is an important question, and study results are mixed. In the CASH study, the protective effect of OC use persisted for women who discontinued using OCs 15 years before participation in the study (*4*).

### Ovarian Cancer

Many case-control studies have examined the association between prior use of OCs and ovarian cancer, primarily epithelial cancers (*14–26*). Except for a small series of women in Utah reported by Risch et al. (*23*), all studies showed a decreased risk among OC users, averaging about 40%. Reports from major cohort studies of OC use are consistent with these results (*12*, *13*, *27*). OCs also appear to protect against borderline ovarian tumors (tumors of low malignant potential) (*28*).

The fact that epithelial ovarian tumors may be more common in less fertile women must be considered in interpreting results of studies, because it could lead to a spurious protective effect of OC use. This explanation is unlikely to account for the lower risk among OC users. The risk of ovarian cancer clearly decreases with increasing duration of OC use (*15*, *22*, *25*, *26*), and this dose-response effect seems independent of parity (*25*, *26*). Protection appears to be long lasting (*21*, *22*, *25*, *26*). In the CASH study, women who first used OCs 10 years or more before participating in the study had about 50% the risk of nonusers (*22*). This study also examined risk associated with each of several specific OC formulations and found similar protective effects for each (*29*).

The risk of ovarian cancer is decreased by any pregnancy, whether complete or incomplete. Casagrande et al. (*15*) suggested that this protection, as well as that provided by OC use, results from the suppression of ovulation. After combining periods of pregnancy and OC use into a single measure of "protected time," the risk of ovarian cancer decreased as protected time increased.

### Breast Cancer

Numerous epidemiological studies have examined the relationship between OCs and the risk of breast cancer. Kelsey and Hildreth (*30*) and Kalache et al. (*31*) provide summaries of early studies. Although results have been published for seven cohort studies and more than 20 case-control studies, the possible relationship between OC use and breast cancer continues to be a major source of controversy (*32–38*). Several studies were begun in the late 1960s, only a few years after OCs became available for clinical use. Unlike the consistent protective effects of combination OCs on the risk of endometrial and ovarian cancer, no clear trend across studies for breast cancer is evident. If one can draw any conclusion from these early studies, it is that OCs do not protect against breast cancer. Furthermore, use during the postmenarcheal period and the perimenopausal period may increase risk. In addition, certain categories of women may have increased risk of breast cancer after use of OCs, such as women with prior benign breast disease, women with a positive family history, and nulliparous women.

**Perimenopausal period.** Five studies have reported an elevated risk of breast cancer with use of OCs around menopause, although the range of risk estimates is wide (*39–43*). A possible explanation for this increased risk is that OCs produce a hormonal state approximating that of a normally menstruating woman, masking the onset of menopause by artificially prolonging menstrual life. The net effect of such use is greater hormonal exposure to estrogens and progestogens than would have occurred naturally during the perimenopausal period.

**Postmenarcheal period.** The second group of OC users who may be at increased risk of breast cancer are women who have used OCs for long periods early in menstrual life, particularly before their first full-term pregnancy. Because prolonged use by very young women is a recent phenomenon, only the most recently conducted studies may have been able to measure such an effect. We review results from major case-control studies completed in the 1980s that have either examined breast cancer risk associated with early OC use in women under age 45 years or provided subgroup results for these women (*44–59*; table 1). These studies have produced conflicting results. However, a greater consensus appears in the latest reports from Europe and the United States.

Design aspects of the studies may account for some of the early discrepant results. The studies have varied in terms of the source of case and control subjects, matching criteria used in selecting control subjects, and method of interview. The early hospital-based studies that used patients with diseases and conditions thought not to be related to OC use as control subjects may have produced biased risk estimates. A survey conducted in the United States during the early 1970s showed that OC users were 20%–40% more likely to be hospitalized for non-life-threatening conditions than were nonusers (*60*). This bias would have resulted in underestimates of the true strength of the association between OC use and breast cancer. No similar data on OC use by women admitted to hospitals have been published for the 1980s. The degree of age matching has varied from matching on exact year of birth (*53*, *56*) to no age matching (*48–52*, *55*). Close age matching is critical because cohort trends in OC use before age 25 years and before the first full-term pregnancy have been reported (*61*). In-person interviews with subjects are preferable to telephone interviews because in-person interviews allow the use of photographs of OCs and a calendar to facilitate accurate recall of dates of OC use and formulations used.

The largest of the "negative" studies (ie, studies that show no increased risk of breast cancer in young women associated with OC use) is the CASH study, which was conducted simultaneously in eight areas of the United States (*48–51*). For women under age 45 years, no increased risk was found for any duration of OC use or for OC use before first full-term pregnancy (*42*). In a later publication, an excess risk associated with OC use was reported among the small subgroup of nulliparous women under age 45 years who had menarche before age 13 years (*50*). Peto (*37*) noted an apparent contradiction with the earlier publication, calculating that women with at least 4 years of use had a significantly elevated relative risk of 1.48, compared to the previously reported estimate of 1.2. These discrepant results are probably due to differences in stratification and the methods of adjustment for other

variables. Analyses of specific formulations (restricted to women using only one formulation) found no appreciable variation in relative risks associated with the estrogen component of OCs (*62*). Although nulliparous women who used mestranol exclusively appeared to be at increased risk, no trend with longer use, time since first use, or time since last use was observed.

A British study of women younger than 36 years at breast cancer diagnosis and age-matched control subjects showed a highly significant trend in risk of breast cancer was associated with longer OC use (*56*, table 1). Use before and after first full-term pregnancy showed similar significant trends in risk with longer use. Although few women had long-term use of OCs with less than 50 μg of estrogen, the results suggest that use of low-dose OCs is associated with lower risk of breast cancer than use of pills with greater estrogen content.

**Table 1.**—Case-control study results regarding relationship between oral-contraceptive (OC) use and breast cancer risk in young women

| First author and year (Ref.) | Location of study | Age range of subjects, y | Duration of OC use | Relative risk |
|---|---|---|---|---|
| Negative studies | | | | |
| Vessey et al., 1983 (*44, 45*) | United Kingdom | 16–35 | 1–12 mo | 0.8 |
| | | | 13–48 mo | 0.8 |
| | | | 49–96 mo | 1.6 |
| | | | ≥97 mo | 1.0 |
| Miller, 1986 (*46, 47*) | United States | 20–45 | 1–11 mo* | 0.7 |
| | | | 1–2 y | 1.4 |
| | | | 3–4 y | 0.8 |
| | | | 5–6 y | 1.5 |
| | | | ≥7 y | 1.4 |
| Stadel et al., 1989 (*48–51*) | United States | 20–54 | 1–47 mo | 1.1 |
| | | | 4–7 y | 1.2 |
| | | | 8–11 y | 1.2 |
| | | | ≥12 y | 0.9 |
| Paul et al., 1986 (*52*) | New Zealand | 25–34 | 1–23 mo | 2.8 |
| | | | 2–5 y | 1.6 |
| | | | 6–9 y | 1.8 |
| | | | ≥10 y | 4.6 |
| | | 35–44 | 1–23 mo | 0.9 |
| | | | 2–9 y | 0.9 |
| | | | ≥10 y | 0.8 |
| Positive studies | | | | |
| Meirik et al., 1986 (*53*) | Norway and Sweden | <45 | 1–47 mo | 1.1 |
| | | | 4–7 y | 1.2 |
| | | | 8–11 y | 1.4 |
| | | | ≥12 y | 2.2 |
| McPherson et al., 1987 (*54*) | United Kingdom | 16–44 | 1–47 mo | 1.1 |
| | | | 4–12 y | 1.2 |
| | | | >12 y | 1.8 |
| Miller et al., 1989 (*55*) | United States | 25–44 | <3 mo | 2.5 |
| | | | 3–11 mo | 1.8 |
| | | | 1–4 y | 1.8 |
| | | | 5–9 y | 1.9 |
| | | | ≥10 y | 4.1 |
| UKNCCSG 1989 (*56*) | United Kingdom | <36 | 1–48 mo | 1.0 |
| | | | 49–96 mo | 1.4 |
| | | | ≥97 mo | 1.7 |
| Bernstein et al., 1990 (*57–59*) | United States | <38 | 1–48 mo | 0.9 |
| | | | 49–96 mo | 1.1 |
| | | | ≥97 mo | 1.7 |

UKNCCSG, United Kingdom National Case-Control Study Group.
*Data available only on use before first birth.

The results of these studies suggest that long-term use of OCs confers at least a 50% increase in breast cancer risk. Because both timing of menarche and timing of first full-term pregnancy are critical risk factors for breast cancer, exposure between these two events may also be critical for establishing breast cancer risk. The period immediately after onset of menses is characterized by frequent anovular cycles (*63*), and even when ovulatory cycles occur in adolescent girls, they are characterized by significantly lower levels of estradiol and progesterone than are those of fertile adult women (*64*). Therefore, OC use during the postmenarcheal years may expose young women to higher levels of estrogens and progestogens than would have occurred naturally, altering their subsequent risk of breast cancer. Logically, this exposure would occur if a young woman's average breast tissue mitotic activity when on OCs was greater than her average "normal" mitotic activity and could be due to either the estrogen or the progestogen component of the compound. Similarly, low-dose OCs could be expected to protect against breast cancer in regularly ovulating women.

### Cervical Cancer

Although the relationship between OCs and cervical neoplasia has also been studied, several factors complicate interpretation of the results. Sexual factors are risk factors for cervical cancer that may also be associated with the use of OCs, with OC users more likely to have been younger at first sexual intercourse or to have had more sexual partners than nonusers (*65*, *66*). Smoking is another possible confounder of the cervical cancer–OC association. Barrier methods of contraception are protective against cervical neoplasia, which further complicates the analysis of risk associated with OC use, because women who use these methods will be less likely to have used OCs (*67–71*).

### Liver Tumors

Because of the rarity of primary liver cancer, few analytic studies have been conducted investigating the risk associated with OC use. Henderson et al. (*72*) reported on 11 cases of hepatocellular carcinoma in young women and compared their OC use to that of 22 age-matched neighborhood control women. Ten patients had used OCs for 6–168 months. The other patient had received multiple "hormone" shots of undetermined type for regulation of menstrual periods during the 9 months preceding diagnosis. Six of the 11 patients were taking hormones at the time of diagnosis. On average, patients used OCs significantly longer than did control subjects (65 vs. 27 months).

OC use by 26 women under age 50 years and diagnosed with hepatocellular carcinoma (*73*) was compared with use by control subjects from the London/Oxford breast cancer case-control study (*44*, *45*). Short-term OC use was not associated with increased liver cancer risk; however, use for 8 years or more was associated with a significantly elevated relative risk of 4.4. When the case group was restricted to women without markers of hepatitis B infection, the relative risk remained significantly elevated (relative risk 7.2) in the long-term users. A case-control study of young women (aged 20–44 years) who died of cancer of the liver showed that use of OCs was associated with a significantly elevated relative risk of hepatocellular carcinoma of 3.8 and that use for 8 years or more was associated with a significantly increased relative risk of 20.1 (*74*). No apparent increase in risk was found for cholangiocarcinoma in association with OC use. Studies from Italy (*75*) and the United States (*76*) also provided evidence that OCs may cause liver cancer.

The World Health Organization (WHO) Collaborative (case-control) Study of Neoplasia and Steroid Contraceptives, conducted primarily in areas where hepatitis B is endemic and background rates of liver cancer are relatively high, found no evidence that short-term use of OCs increased liver cancer risk (*77*). Unfortunately, no data on hepatitis B status of the subjects were collected.

## INJECTABLE CONTRACEPTIVES

Depot-medroxyprogesterone acetate (DMPA), a progestogen, is a long-acting injectable contraceptive that is used in many areas of the world. Although not approved for general use as a contraceptive by the US Food and Drug Administration (*78*), the drug is marketed in more than 70 other countries (*79*). By the early 1980s, approximately 2 million women worldwide were current users of DMPA (*80*). The concern about possible carcinogenic effects of DMPA use stems partly from the results of animal studies, which have found increased numbers of malignant breast nodules in female beagles (*81*, *82*) and endometrial carcinoma in rhesus monkeys (*83*). Epidemiological data related to cancer risk associated with use of DMPA are limited, and only breast cancer data are reviewed here.

One record-linkage study conducted in Atlanta, Georgia, matched family-planning clinic records of approximately 5000 women who had used DMPA with hospital admission records to ascertain cancer incidence (*84*). Most women in this study received DMPA for less than 1 year; fewer than 13% had used DMPA for more than 3 years. A problem with this study was an estimated 45% underascertainment of cancer in the cohort, although an attempt was made to adjust for this fact in the statistical analysis. Seven cases of breast cancer were identified in this study, compared with 10.1 expected after adjustment for the lack of complete follow-up.

The ongoing WHO study is evaluating cancer risk associated with use of DMPA and with use of OCs. This study reported on 427 women diagnosed with breast cancer, of whom 39 had ever used DMPA (*85*). The relative risk adjusted for potential confounders was 1.0. The trend in risk of breast cancer associated with longer DMPA use was essentially flat, although this trend was based on a maximum duration-of-use category of 36 months or more.

Lee et al. (*86*) reported a statistically significant increased risk of breast cancer associated with DMPA use in Costa Rica (relative risk 2.6). Risk was elevated for each duration-of-use category evaluated up to 6 years (<12

months, relative risk 2.3; 12–23 months, 4.4; 24–71 months, 3.4); there were no case and four control subjects in the 72 months-of-use or more group. Similarly, Paul et al. (*87*) reported results of a case-control study of breast cancer in women aged 25–54 years in New Zealand. Although no overall increased risk of breast cancer was observed (relative risk 1.0), there was a twofold increased risk of breast cancer associated with DMPA use in the youngest age-group (25–34 years of age). Furthermore, the relative risk was greatest for women in this age-group who had used the drug for 6 years or more, although there were few women in this category.

If estrogens alone are a cause of breast cancer, then DMPA should decrease breast cancer risk because the regimen prevents ovulation and does not include any exposure to exogenous estrogen. This does not happen. In fact, the results of the studies from Costa Rica and New Zealand suggest that progesterone may act like estrogen to stimulate breast cell growth.

## HORMONE-REPLACEMENT THERAPY

By the mid-1970s, over 28 million prescriptions of noncontraceptive estrogens were being filled annually in the United States. Due to concerns about the carcinogenic potential of ERT on the breast and endometrium, the number of estrogen prescriptions declined by 50% by 1980. Hence, a cyclic estrogen-progestogen regimen became widely recommended and prescribed. By 1986, prescriptions of estrogen had increased to 20.3 million, and compared with 1981, progestogen prescriptions, exclusive of OCs, had increased more than 50% (*88*).

The advisability of long-term use of ERT for postmenopausal women remains controversial. This controversy centers around three issues: the potential benefits to be derived from such therapy compared with the potential risks, the most favorable dosage to maximize the benefit-risk ratio, and the benefits and risks to be derived by adding a progestogen to ERT.

### Endometrial Cancer

Case reports of endometrial cancer occurring in women after the use of estrogens have appeared in the medical literature for more than 30 years, but there have been serious controlled efforts to study this relationship only since 1975. Nearly all studies demonstrated a strong association between estrogen use and disease risk that was related to both dosage and duration of use (*89–92*). The benefit of adding a progestogen to ERT to reduce estrogen-induced endometrial mitotic activity has been clearly established in clinical practice (*93–95*). However, there are few epidemiological data on the risk of endometrial cancer in women using this combination therapy. It has been suggested that the progestogen dose should be the lowest possible to achieve the desired histological changes in the endometrium because of the potential for adverse effects on risk of heart disease and breast cancer (*96*). Whitehead et al. (*97*) showed that duration of progestogen therapy is more important than dosage in inducing a secretory endometrium; however, the optimal type, dose, and duration of progestogen have not been established for minimizing endometrial cancer risk.

### Ovarian Cancer

Data on ovarian cancer risk associated with ERT are sparse in that most studies have been based on relatively few cases. Available results generally indicate that menopausal estrogens do not alter risk (*30*).

Weiss et al. (*98*) and LaVecchia et al. (*99*) examined risk by histological type of tumor and observed elevated relative risks (3.1 and 2.3, respectively) for endometrioid carcinoma of the ovary related to noncontraceptive estrogen use that were of borderline statistical significance. Cramer et al. (*100*) also found a higher proportion of estrogen users among women with endometrioid tumors. Histologically, these tumors resemble adenocarcinoma of the endometrium.

No data are available regarding the effect of combined HRT on risk of cancer of the ovary. If any possible increase in risk due to ERT is restricted to endometrioid tumors, then the addition of a progestogen might counteract the effects of estrogen.

### Breast Cancer

Hoover et al. (*101*) conducted the most credible uncontrolled follow-up study on the possible effects of ERT on risk of breast cancer. Although they reported only a 25% excess of breast cancer in their cohort of menopausal estrogen users compared with the number expected based on general population rates (49 observed vs. 39 expected), they did report a more substantial excess among women using high doses for a long time.

Early case-control studies that reported findings on menopausal estrogens and breast cancer were often limited by low statistical power, insufficient data on dosage and duration of use, and the possibility of bias. Case-control studies with healthy control subjects found small to moderate increases in risk of breast cancer after long-term use, although some variation across studies exists with respect to the ovarian status (intact ovaries vs. ovaries removed) or hysterectomy status (surgical vs. natural menopause) of subgroups at elevated risk (*102–109*; table 2).

A cohort study of Swedish women 35 years of age or older who had been prescribed noncontraceptive hormones reported a 70% elevation in risk with long-term use of estrogen alone (estradiol valerate) (*110*). However, survival analyses comparing breast cancer patients within this cohort of estrogen-treated women with breast cancer patients with no recorded ERT suggest a relative survival advantage in estrogen-treated women (*111*). This advantage was restricted to women who were diagnosed with breast cancer while actually on ERT or who had stopped therapy in the previous 12 months.

Results regarding the risk of breast cancer associated with postmenopausal hormone use among a cohort of nurses who are being followed prospectively were pre-

**Table 2.**—Results regarding relationship of estrogen-replacement therapy and breast cancer in case-control studies with population control subjects

| First author and year (Ref.) | Type of menopause | Relative risk | | |
|---|---|---|---|---|
| | | Ever used | Long-term use | |
| Ross et al., 1980 (*102*) | NM | 1.4 | TMD>1500 | 2.5 |
| | BSO | 0.8 | TMD>1500 | 0.7 |
| Hoover et al., 1981 (*103*) | NM | 1.3 | | |
| | BSO | 1.5 | 5+ y | 1.7* |
| Hulka et al., 1982 (*104*) | NM | 1.8 | 10+ y | 1.7 |
| Hiatt et al., 1984 (*105*) | BSO | 0.7 | 3+ y | 1.8 |
| Nomura et al., 1986 (*106*)† | NP,J | 1.1 | 6+ y | 1.9 |
| | NP,C | 0.9 | 6+ y | 1.3 |
| Brinton et al., 1986 (*107*) | NM | 1.1 | 15+ y | 1.7 |
| | BSO | 1.1 | 15+ y | 1.4 |
| McDonald et al., 1986 (*108*)‡ | NM | 0.8 | 6+ y | 0.7 |
| | BSO | 1.3 | 6+ y | 1.2 |
| Wingo et al., 1987 (*109*) | NM | 0.8 | 5+ y | 0.7 |
| | BSO | 1.3 | 15+ y | 1.7 |

NM, natural menopause; BSO, bilateral salpingo-oophorectomy; TMD, total milligram accumulated dose; NP, detail not provided; J, Japanese; C, Caucasian.

* Duration based on years between issuance of first and last prescription. Long-term-use relative risk is adjusted for type of menopause.

† Twenty percent of subjects were premenopausal.

‡ Ever users are women who have used estrogens for at least 1 year; ever users and long-term users are compared to women with either <1 year or no estrogen use.

sented for past users and current users separately (*112*). Although the results for past use related to all hormone use, most women used conjugated estrogens unopposed by progestogens. Among past users of HRT, there was no increased risk of breast cancer in any duration-of-use category. However, these results must be interpreted with caution because no adjustment was made in the analysis for age at menopause, and age at menopause must be negatively correlated with duration of HRT use (*113*). Among current users, breast cancer risk was significantly elevated.

In the 6-year follow-up of a cohort of Seventh-Day Adventist women, any use of HRT (primarily ERT) was associated with a statistically significant 69% increase in breast cancer risk (*114*). However, there was no strong dose-response effect with increasing duration of use.

Hunt et al. (*115*) reported on the relationship between breast cancer incidence and mortality in a cohort of 4544 British women receiving HRT at specialist menopause clinics. The average duration of HRT use per woman was 67 months, which was roughly equally divided between ERT and combination therapy. Overall, the observed incidence of breast cancer was 59% higher than expected based on national incidence data (50 observed cases vs. 31 expected). Women using unopposed estrogen for 4 years or more had 2.4-fold greater risk than those who never used ERT. Despite the higher-than-expected incidence of breast cancer, these investigators reported a 45% reduction in breast cancer mortality among women using all types of HRT. However, the latter analysis appears to have been seriously flawed (*116*), because the comparison population, unlike the study population, included prevalent as well as incident breast cancer patients.

Based on the overall evidence from recent case-control studies with population control subjects and from cohort studies, long-term use of ERT may carry with it an increase in breast cancer risk. The effects on breast cancer risk of adding a progestogen to ERT have not been well evaluated. In the Swedish cohort, women who received only combined estrogen-progestogen treatment had a 4.4-fold greater risk of breast cancer with more than 6 years of use than women with no history of HRT use; however, there was no evidence of an effect with shorter-term use, and this estimate was based on only 10 patients (*110*).

Nonetheless, these results for combination therapy are compatible with the results of the most recent studies of DMPA and breast cancer described above and together suggest that progesterone may enhance the carcinogenic effect of ERT on the breast. Unlike the endometrium, for which maximal mitotic activity occurs during the follicular phase of the menstrual cycle, cell replication in breast epithelium peaks in the luteal phase (*117*). This phenomenon suggests that progesterone in conjunction with the luteal-phase estradiol peak could stimulate breast tissue mitotic activity and increase breast cancer risk.

### Other Health Effects

There is substantial epidemiological and clinical evidence that estrogens prevent osteoporosis and its most serious medical consequence, hip fracture (*118*, *119*). Women using estrogens for 5 years in the postmenopausal period approximately halve their risk of sustaining a nontraumatic osteoporotic fracture. Case-control and cohort studies have provided compelling evidence that estrogens lower risk of coronary heart disease (*120*). This effect is probably mediated through raised high-density and reduced low-density lipoprotein cholesterol levels in estrogen users. Because death rates from coronary heart disease among women in the United States are four times those from breast and endometrial cancer combined, this benefit alone could far outweigh any carcinogenic potential (*96*).

## HORMONAL PREVENTION OF BREAST CANCER

### Luteinizing-Hormone-Releasing Hormone

Clearly, OC use provides significant protection against ovarian cancer (presumably by preventing ovulation) and endometrial cancer (presumably by delivering only opposed estrogen to the endometrium). OCs do not, however, provide protection against breast cancer, presumably because they deliver estrogen plus progestogen to the breast in quantities sufficient to replace the action of the natural estrogen plus progesterone of the normal menstrual cycle.

OCs have two functions. The first is to stop ovulation (by interfering with feedback mechanisms), which may be considered as the induction of a temporary artificial menopause. The lack of menopausal symptoms (and other adverse side effects of failed ovarian function) in women using OCs is explained by the second function, ie, as a form of HRT. The ovulation-inhibiting function of OCs can be achieved with a luteinizing-hormone–releasing hormone agonist (LHRHA), and such a formulation of hormones may be optimal to prevent the adverse effects of stopping ovarian function.

LHRHAs can be administered at a dose sufficient to completely eliminate ovarian steroid production (*121*, *122*). Similar to the effect of OCs, the effect of LHRHA use on ovarian function appears to be completely reversible, and use of such compounds as a contraceptive in the premenopausal period could achieve major reductions in a woman's risk of breast, endometrial, and ovarian cancer (*123*). Such LHRHA-induced inhibition of ovulation will, however, be associated with major harmful side effects (*121*, *122*)—the same side effects that are associated with natural (or surgically induced) menopause. In particular, hot flushes, significant bone loss, an increase in low-density lipoprotein cholesterol, and, almost certainly, a significantly increased risk of cardiovascular disease may result from their sole use (*96*, *124*). Present-day OCs could be added to the LHRHA regimen to obviate these side effects, but this would, of course, achieve little over what could already be achieved by use of the OCs alone.

Extensive experience with estrogen-progestogen preparations in dosages lower than those typically found in OCs has been gained through use of HRT. Experience with ERT shows that the harmful side effects of LHRHA use would probably be eliminated with the use of 0.625 mg/d of conjugated equine estrogen or its equivalent (*123*, *125*). Table 3 shows the predicted relative risks for breast cancer of using LHRHA plus conjugated equine estrogen at 0.625 mg/d for 21 days during each 28-day-cycle regimen for 5, 10, or 15 years at premenopausal ages; these relative risks are calculated assuming that the computed effective mitotic rates of postmenopausal women on ERT would apply to a premenopausal woman taking LHRHA plus ERT (*126*). Based on this model, this regimen would reduce lifetime breast cancer risk by nearly 35% if used for only 5 years, by 55% if used for 10 years, and by more than 70% if used for 15 years.

**Table 3.**—Predicted relative risks of breast cancer in women using luteinizing-hormone–releasing hormone agonist plus 0.625 mg conjugated equine estrogen/d for 21 days during 28-day treatment*

| Duration of regimen (y) | Relative risk (users vs. nonusers) |
|---|---|
| 5 | 0.68 |
| 10 | 0.45 |
| 15 | 0.28 |

*Based on breast tissue aging model (*126*) with menarche at 13 y, first full-term pregnancy at 22 y, menopause at 50 y; relative risks evaluated at age 70 y assuming regimen is used at any time after first full-term pregnancy and before age 40 y.

### Tamoxifen

Tamoxifen (Nolvadex), at the doses (20–40 mg/d) given as breast cancer therapy, acts as an antiestrogen in breast cancer cells and is commonly administered as an adjuvant therapy to postmenopausal women with breast cancer. An overview of the many randomized trials of tamoxifen in the treatment of breast cancer showed a significant reduction in mortality in tamoxifen-treated women over the age of 50 years (*127*). Although the results were not separately statistically significant, the improved survival was evident in positive- and negative-node patients and in women with estrogen receptor-rich and receptor-poor tumors.

A reduced risk of contralateral primary breast cancer has also been reported in women receiving adjuvant tamoxifen. The results of the studies showed a 38% reduction in risk of contralateral primary breast cancer (*128*). This effect may be even larger in women given tamoxifen continuously, ie, women for whom tamoxifen treatment was not stopped after a few years. Although tamoxifen is commonly considered an antiestrogen because of its effects on breast cancer, it appears to act as an estrogen in many other tissues, and, in particular, it appears to have estrogenic effects on cholesterol and bone metabolism and on the vaginal epithelium. Therefore, tamoxifen may be an acceptable form of HRT for women with a history of breast cancer (*128*). It appears that tamoxifen may be as good as conjugated equine estrogen or other traditional estrogens in providing a reduced risk of bone loss and arteriosclerotic cardiovascular disease while reducing the risk of breast cancer (*128*).

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# Health Risks Associated With Excessive Warnings About Alleged Cancer Risks

**Elizabeth M. Whelan**[1]

**ABSTRACT—As the adage states, "when everything is dangerous, nothing is." If the word *carcinogen* (cancer-causing agent) is used to designate a spectrum of products, chemicals, and other environmental exposures, then the classification *cancer causing* when referring to the results of human epidemiological studies becomes meaningless. Thus, the emerging "carcinogen-of-the-week" phenomenon is counterproductive in preventing the toll of human cancer in that it diverts attention from real causes. [J Natl Cancer Inst Monogr 12:149–151, 1992]**

Americans who become convinced that everything causes cancer feel helpless and hopeless—so why not smoke cigarettes? If smoking does not give an individual cancer, then surely eating apples with Alar will. Scientists should urge members of the media who report on health and the environment to distinguish among 1) known causes of cancer, ie, causes determined by epidemiological studies; 2) suspected causes, based on limited human observations but not yet confirmed; and 3) rumors, ie, alleged causes for which there is no human epidemiological evidence of cause but only observations of increased cancer risk in laboratory animals.

Data on the health risks associated with excessive warnings about the alleged risks of cancer are necessarily limited. I review the risks associated with issuing too many warnings about the alleged causes of cancer and explore a related question: Why is the most educated, most health-conscious society in the world receiving so many hypothetical warnings about alleged cancer risks?

## RISK OF TOO MANY RISKS

When everything is declared to cause cancer, then nothing seems to. When the word *carcinogen* is repeatedly used to designate anything and everything that causes cancer at high doses in laboratory animals, then *carcinogen* used in relation to observations of human epidemiology becomes diminished in importance.

In the past few decades, Americans have been subject to dozens of warnings about carcinogens. Perhaps the first one was the cranberry scare of 1959. Just days before Thanksgiving, a representative of what is now the Department of Health and Human Services declared that a chemical (aminotriazole) used in the cranberry bogs caused cancer in laboratory animals (*1*). For most Americans, Thanksgiving dinner was served without the sauce that year. During the next three decades, there were many other cancer scares, eg, nitrite in bacon, various chemicals in hair dye, cyclamate and saccharin, and, most recently, Alar, an agricultural chemical used to regulate the growth of apples (*2*). All these cancer warnings had at least one thing in common: They were based on the observation that high-dose exposure of laboratory rodents to the chemical in question caused an increase in cancer in the animals. There was no evidence in these cases that human cancer risk was elevated. Indeed, at least in the case of saccharin, there was human epidemiological evidence (based on studies of diabetic patients who consumed a substantial amount of the sweetener) that there was no known increased cancer risk in humans, even at high doses (*3*).

### Consumer Products Containing Carcinogens

Several consumer products illustrate my concerns about the risks associated with too many cancer risks.

1. Liquid Paper typewriter correction fluid is a product of the Gillette Company of Boston. About 2 years ago, the state of California, in its attempt to reduce the cancer toll in that state, banned the product (*4*). Under a law known as Proposition 65 (*5*), any product that contains even a trace level of a chemical that, at high doses, causes cancer in animals must be banned or at least labeled. An environmental group charged that this product was a carcinogen because it contained a small amount of trichloroethylene as a solvent. The product was banned, and Gillette was fined.

2. A popular insect spray was taken off the market to "protect us from cancer" because it contained 2,3,4,5-*bis* (2 butylene).

3. Approximately half of the US water supply is fluoridated, and many dental rinses, toothpaste, and other products that contain small levels of fluoride are available. However, recent studies in rodents suggest that high-dose exposure (79 ppm) of fluoride increases the risk of osteosarcomas (*6*). As a result, fluoride is being considered by some as a carcinogen, and the Environmental Protection Agency has given some regulatory attention to this matter, despite the facts that the level of exposure in fluoridated water is low (~1 ppm) and there is no evidence that fluoride is a human carcinogen, particularly at the minuscule levels of exposure (*7*).

[1] American Council on Science and Health, 1995 Broadway, New York, NY 10023.

4. Coffee filters are now being called carcinogens (as are paper towels) by some in the media because they contain trace levels of dioxin, a chemical that causes cancer in rodents exposed to large doses.

5. Recently, DowBrands agreed to remove a spot remover from the market because environmental groups charged that it contained trace levels of the "carcinogen" perchloroethylene.

6. Cigarettes do not, to my knowledge, cause cancer in laboratory animals but are responsible for between 30% and 40% of the cancers that occur in humans in the United States each year.

Thus, there is a mixture of the real causes (cigarette smoking) versus the hypothetical causes (those that cause cancer only in laboratory animals) of cancer. This is the risk of too many risks. Consumers become bewildered and indeed suffer from a form of cancer nosophobia, ie, a morbid dread of cancer wherein individuals invest their energies in cancer prevention on hypothetical factors.

## DANGERS OF OVERSTATING HYPOTHETICAL RISKS

The risks of overstating hypothetical risks are multidimensional. First, when so much attention is given to hypothetical risks, there is limited time, energy, and resources to direct to the real causes of cancer, including cigarette smoking, excessive exposure to solar radiation, and alcohol abuse, particularly in conjunction with smoking. Second, there is a risk of removing health-promoting products (eg, fluoride) from the market in an effort to remove any chemical that causes cancer in animals.

## RECOMMENDATIONS

1. Consumers should be encouraged to focus on the real and not the hypothetical causes of cancer.

2. Members of the media, in reporting on alleged cancer-causing effects of environmental chemicals and other factors, should clearly distinguish between human epidemiology and laboratory data, noting the limitations of the latter in extrapolation to human cancer risk.

3. Regulatory agencies (including the US Food and Drug Administration and the Environmental Protection Agency) should be more prudent in interpreting animal experiments and avoid automatic assumptions that high-dose exposure to chemicals by animals necessarily means that low-dose exposure by humans poses risks (*8*).

Instead of seeking zero human exposure to chemicals that in high doses cause cancer in animals, regulatory policies should allow prudent human exposure to animal carcinogens.

## CONTROL OF PUBLIC PERCEPTION OF RISK

Why is the most educated, health-conscious society in the world focusing so much attention on hypothetical risks? Why do the media report so often on animal carcinogens and relatively infrequently about human carcinogens?

First, human beings are apparently willing to avoid being introspective about the causes of disease, preferring to blame someone else, eg, industry, for ill health rather than examine the contribution of individual life-style to disease risk. It is easier to be concerned about dioxin in paper towels than it is to worry about the effects of cigarette smoking.

Second, people seem willing to assume enormous risks with the belief that they are within their own control (eg, those who argue they "choose" to smoke) yet will not tolerate the most minuscule risks perceived as outside their control (eg, pesticide residues in food). Thus, substantial attention is given to remote, hypothetical risks that divert individuals from examining their own life-style factors (*9*).

Third, the manufacturers of the leading cause of cancer, ie, the tobacco companies, are literally getting away with murder. With an advertising and promotion budget in excess of $3.5 billion, tobacco manufacturers have been able to interrupt what should be a free flow of information about the dangers of smoking. For example, there has never been a significant article about the dangers of smoking in any major US magazine that carries cigarette advertisements (which is most US magazines) (*10*, *11*).

The Secretary of Health and Human Services learned about the interruption in the free flow of information recently when his speech to the Republican Governors Association was cancelled because his remarks contained a reference to the health dangers of smoking. The conference was sponsored by R.J. Reynolds (*12*). I have encountered censorship on the subject of the dangers of smoking. Recently, I was invited to the annual meeting of the Grocery Manufacturers Association to speak on the overstated cancer risk of agricultural chemicals like Alar and the exaggerated coronary heart disease risk caused by substances such as tropical oils. At the last moment, I was asked to avoid the word *cigarette* because I might offend the food companies in the audience that were owned by cigarette companies (including General Foods, Kraft, and R.J. Reynolds/Nabisco). Because it is impossible to discuss why Alar does not cause cancer and tropical oils do not cause heart disease without discussing what does pose a risk of heart disease and cancer, I had to withdraw from the speaking engagement.

The role of the cigarette industry in keeping the bad news about cigarettes out of newspapers and magazines cannot be overstated. The end result is more attention to nonrisks. For example, in seeking a public relations firm for the American Council on Science and Health, I encountered the long arm of the tobacco industry. I interviewed many firms that claimed they place many of the stories that appear in the US media. They said they would gladly represent my group as long as we never asked them to place a pejorative story about the health effects of smoking, because it would alienate their cigarette clients. Thus, these firms regularly send out stories about the

"causes" of cancer and systematically edit out any reference to smoking.

## CONCLUSION

I observed an event 2 years ago that riveted my attention to the seriousness of this problem. In February 1989, the Natural Resources Defense Council in conjunction with CBS's "60 Minutes" released a report indicating that children in the United States were at "intolerable risk" of cancer because they consumed apple products that had been exposed to Alar. The nation took this report seriously and "apple anxiety" was rampant.

A few days after this report, I presented a lecture on the dangers of smoking to a private elementary school in New York City. When I completed my discussions on the cancer-causing effects of smoking, one 4th grader said, "I just watched them throw 450 pieces of apple pie into the dumpster in the cafeteria because apples cause cancer. So what is your point about cigarettes causing cancer?" This incident clearly reflects the risks of overstating hypothetical cancer risks.

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# Dietary Recommendations for Cancer Prevention: Public Policy Implementation

Marion Nestle[1]

**ABSTRACT—Dietary recommendations for cancer prevention advise reduced intake of fat; increased intake of fruits, vegetables, and grains; and moderate intake of alcohol and salt-cured, salt-pickled, and smoked foods. These recommendations are virtually identical to those issued by public health agencies for the prevention and treatment of coronary heart disease, diabetes, hypertension, and other chronic diseases, as well as for the health promotion of the general public. The consensus on these recommendations suggests the need for public policies to promote their implementation. These policies should be designed not only to encourage improvements in the dietary knowledge, attitudes, and behavior of individuals but also to address environmental and institutional barriers to dietary change. [J Natl Cancer Inst Monogr 12:153–157, 1992]**

Since the late 1970s, various federal agencies and private health organizations have issued dietary recommendations designed to reduce cancer risk. These recommendations have elicited—and continue to elicit—intense controversy, mainly over the reliability of the scientific evidence on which they are based. This controversy contributes to public confusion about the role of dietary factors in cancer causation and is one source of the misperception that "everything we eat" may cause cancer.

This confusion is unfortunate, because it obscures the virtually unanimous agreement about basic dietary principles for prevention of cancer and other leading causes of death and disability in the United States. It also obscures the growing consensus among public health groups that a consistent set of dietary changes should reduce overall risks for chronic diseases in the population.

As the universal applicability of common dietary principles has become increasingly recognized, the focus of dietary guidance has shifted from the need to design appropriate recommendations to their implementation. This new focus emphasizes the identification of more effective ways to encourage and enable the public to select diets that will reduce the risks of cancer and other chronic diseases.

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## CANCER RECOMMENDATIONS

The first dietary recommendations designed specifically to prevent cancer were issued on an interim basis by the National Cancer Institute (NCI) in 1979 (*1*). To evaluate the research basis of these recommendations, the National Research Council (NRC) conducted a comprehensive review of existing studies that linked dietary factors to cancer risk and published interim dietary guidelines based on that evidence in 1982 (*2*). Despite criticisms that the evidence presented in this report was insufficient to warrant the development of dietary guidelines and that, in any case, dietary risks for cancer were relatively unimportant (*3*), the American Cancer Society (*4*), NCI (*5*, *6*), and the American Institute for Cancer Research (*7*), on the basis of independent research reviews, issued similar dietary recommendations during the next several years. In 1988, NCI issued its current dietary guidelines for cancer prevention, urging Americans to consume more dietary constituents associated with protection against cancer at various sites (eg, fiber, fruits, and vegetables) and to consume less of items associated with increased risk (calories, fat, alcohol, and salt-cured foods) (*8*; table 1).

## RECOMMENDATIONS FOR DISEASE PREVENTION AND TREATMENT

A notable feature of these cancer guidelines is their similarity to dietary recommendations for the prevention or treatment of other chronic conditions. The American Heart Association (AHA) sponsored investigations of the role of dietary fat in development of coronary heart disease in the mid-1950s (*9*) and first recommended restrictions on fat intake in 1961 (*10*). Under AHA auspices, the first formal recommendations for dietary changes and public policies to reduce coronary heart disease risk factors were published in 1970 (*11*); since then, AHA has issued similar recommendations at regular intervals (*12–14*). Similar recommendations, developed at a consensus conference of the National Institutes of Health in 1985 (*15*), form the basis of the dietary intervention strategies of its current National Cholesterol Education Program (*16*). In addition, nearly identical dietary principles have been recommended as the first step in the treatment of hyperlipidemias (*17–19*), hypertension (*20*, *21*), and non-insulin-dependent diabetes mellitus (*22*).

Table 1.—National Cancer Institute dietary guidelines for cancer prevention

| |
|---|
| Reduce fat intake to ≤30% of calories |
| Increase fiber intake to 20–30 g/d, with an upper limit of 35 g |
| Include a variety of vegetables and fruits in daily diet |
| Avoid obesity |
| Consume alcoholic beverages in moderation if at all |
| Minimize consumption of salt-cured, salt-pickled, or smoked foods |

From (*8*).

## RECOMMENDATIONS FOR HEALTH PROMOTION

In 1977, recognition of the fundamental similarity of dietary recommendations for prevention and treatment of cancer, heart disease, and other chronic diseases stimulated a Senate committee to develop *Dietary Goals for the United States* (*23*). These goals were to increase carbohydrate consumption to 55%–60% of energy intake, decrease fat consumption to 30% and saturated fat to 10% of energy, reduce cholesterol to 300 mg/d or less, and reduce salt intake to 5 g/d or less. To achieve these goals, the committee recommended increased intake of fruits, vegetables, and grains and substitution of lean meats and low-fat dairy products for those more commonly consumed.

In the context of current familiarity with these recommendations, it may be difficult to recall the controversy elicited by their release. Food manufacturers were concerned about their potential impact on sales, scientists about weaknesses in the research base, physicians about their necessity for healthy individuals, and nutritionists about their practicality (*24*).

To address these concerns, the Departments of Agriculture and of Health, Education and Welfare initiated the development of a federal consensus statement of dietary guidance policy for healthy adults and children. The resulting *Dietary Guidelines for Americans*, first published in 1980, expressed the recommendations of the *Dietary Goals* in general terms that avoided the use of specific percentage target figures (*25*). The most recent edition of the *Dietary Guidelines* has retained the general phrasing of these statements but includes quantitative targets for fat, saturated fat, and alcohol in the accompanying text (*26*).

In the mid-1980s, in efforts to resolve the scientific aspects of the controversy, two US agencies began to develop major comprehensive reviews of the existing research linking specific dietary factors to specific chronic diseases. The results of these projects were reported in 1988 by the US Public Health Service (USPHS) in the *Surgeon General's Report on Nutrition and Health* (*27*) and in 1989 by NRC in its study, *Diet and Health* (*28*). In 1988, the World Health Organization Regional Office for Europe also reviewed data on diet and chronic disease prevalence among its 32 member nations in the more concise but equally comprehensive report *Healthy Nutrition* (*29*).

The reports of these projects are remarkably similar. Each states the consensus that most evidence supports common conclusions: Diet affects chronic disease risk, dietary changes can reduce this risk, similar dietary changes can reduce risks for multiple chronic diseases, and reduction of fat intake is the principal priority for dietary change. The recommendations in these reports also are consistent, with each other and those of previous reports. To illustrate these similarities, the recommendations of NRC's *Diet and Health* study are listed in table 2.

Thus, dietary recommendations issued by multiple agencies, developed to address various disease conditions and released over at least a 20-year period, have repeated the same basic message: Diets containing less fat and more complex carbohydrates should be recommended to promote health and reduce risks for chronic disease.

## PUBLIC KNOWLEDGE VERSUS BEHAVIOR

Surveys demonstrate that the US public is becoming increasingly aware of this basic dietary message. For example, most respondents in a recent Gallup poll stated that balance, variety, and moderation are the keys to healthy eating (95%), recognized that what they ate might affect future health (83%), and said that the diet should contain 30% or less energy from fat (65%) (*30*). Food industry analysts consider consumer demands for nutrition information, choice of foods perceived as healthy, and rejection of foods perceived as unhealthy as important influences on current trends in food marketing and product development (*31*).

Despite this widespread knowledge of the role of diet in health, the overall dietary patterns of the US population seem to have improved only minimally, if at all. Food availability data (an indirect measure and, usually, an overestimate of actual food consumption) indicate that use of fats and oils increased by 21% between 1971 and 1988. Although the availability of lard and butter declined by 26% during this period, that of vegetable shortenings and oils increased by 39% (*32*). The proportion of energy intake from fat appears to have declined from a peak of about 40% in the 1960s (*33*) but has since remained at a relatively constant 36%–37% (*34*).

Table 2.—National Research Council dietary recommendations for healthy adults and children

| |
|---|
| Reduce total fat intake to ≤30% of calories |
| Reduce saturated fatty acid intake to <10% of calories |
| Reduce intake of cholesterol to <300 mg/d |
| Eat ≥5 servings/d of vegetables and fruits, especially green and yellow vegetables and citrus fruits |
| Eat ≥6 servings/d of a combination of breads, cereals, and legumes |
| Balance food intake and physical activity to maintain appropriate body weight |
| Limit consumption of alcohol to the equivalent of 1 oz pure alcohol/d |
| Limit salt intake to ≤6 g/d |

From (*28*).

Food supply data show an increase in the availability of fruits and vegetables (*32*), but the diets of few Americans appear to meet current recommendations for intake levels of these foods. An analysis of data from the second National Health and Nutrition Examination Survey of 1976–1980 found that 85% of respondents had eaten red meat, which is high in fat, on the day they were surveyed. Although 83% reported eating vegetables (a category that includes potatoes), only 59% reported consuming fruit, and only 28% and 21%, respectively, reported consuming any fruit rich in vitamins C or A, considered especially protective against cancer (*35*). Further analysis of these data revealed that only 9% of respondents had eaten the recommended two fruits and three vegetables on the day they were surveyed and that 45%, 22%, and 11%, respectively, had eaten no fruits, no vegetables, or no fruits or vegetables that day (*36*). More recent data provide little evidence for improvement: Only 33% of respondents to a 1989 survey reported eating at least the recommended five servings of fruits and vegetables on the survey day, and 7% had eaten no fruits and vegetables on that day (*37*).

## BARRIERS TO DIETARY CHANGE

The discrepancy between public knowledge of nutrition and dietary behavior suggests the need for developing more effective public education campaigns (*36*). These campaigns are unlikely to be sufficient, however, unless they also address more fundamental determinants of food intake. For example, surveys of dietary intake routinely demonstrate that higher levels of education and socioeconomic status are associated with better dietary habits (*35–37*).

The present system of food production and marketing also presents substantial barriers to healthy food choices. In 1989, meals consumed outside the home in restaurants or institutions accounted for as much as 45% of the $499 billion in US food sales (*38*). In just the 1 year from 1988 to 1989, spending on away-from-home meals rose by nearly 6% (*39*). The reasons for this trend are well understood by food marketers: Demographic data indicate consistently increasing trends in the numbers of older people, women in the labor force, families headed by single parents, single-person households, and length of the work day—all of which would be expected to promote demands for convenience in meal preparation and food service (*40*).

For many working families, convenience has become a necessity. An estimated 75% of Americans own microwave ovens for rapid cooking, and food manufacturers and fast-food companies are under increasing pressure to provide faster service to customers (*41*). Competition for sales also has increased. Of the more than 9000 new food products introduced in 1989, 1355 were candy and snacks, 1348 were dairy products (eg, novelty ice creams), 1155 were baked goods, nearly 700 were frozen or microwavable meals, and there were 118 new breakfast cereals and 69 new desserts (*42*). Few of these products were designed to meet the dietary guidelines for prevention of cancer and other chronic diseases.

Market forces drive the creation of new foods. US consumers spend only 24 cents of every food dollar on the food itself; the remaining 76% is value added in the form of labor, packaging, transportation, advertising, and, of course, profit (*38*). Advertising alone accounts for 4.5 cents of every food dollar. In 1988, food companies were estimated to have spent $11.5 billion for direct consumer advertising, mainly through electronic and print media, and about twice that much for acquisition of shelf space in retail food stores (*37*). One perspective on the annual food advertising expenditures in the United States is that they could support all of the research, training, and education programs of the NCI for about 5 years.

## AGENDA FOR POLICY IMPLEMENTATION

The challenge to researchers and policymakers concerned about diet and cancer prevention is to find ways to promote healthy eating as a cultural norm, in much the same way as their efforts have led to the institutionalization of smoking-cessation policies. A recent step in this direction is the development by the USPHS of national objectives for diet and cancer prevention to be achieved by 2000. These are 1) to reduce fat intake to an average of 30% of calories or less and average saturated fat intake to less than 10% of calories among people aged 2 years and older and 2) to increase complex carbohydrate and fiber-containing foods in the diets of adults to five or more daily servin gs of vegetables (including legumes) and fruits and to six or more daily servings of grain products (*43*).

Achievement of these objectives will require substantial improvements in the knowledge, attitudes, and behavior of individuals with respect to diet and health. Education is necessary for these improvements, but it is not sufficient. Any new knowledge will need to be supported by policies that reduce barriers to dietary change and that empower people to select healthier diets. *The Surgeon General's Report on Nutrition and Health* urged the adoption of policies to promote education of the public, health professionals, and food service personnel; foster development of incentives and regulations that promote production, marketing, distribution, and sales of low-fat high-fiber foods; and encourage research on the most effective means to implement dietary changes, especially among population groups at highest risk of diet-related chronic disease (*27*).

Implementing these policies will require changes in the dietary behavior of individuals, but it will also require significant efforts of policymakers, scientists, clinicians, educators, consumer advocates, and food manufacturers and marketers to change the environment in which food is consumed (*44*). The development by McDonald's of a new low-fat hamburger is one example of the potential benefits of environmental approaches to dietary change (*45*).

One logical focus for implementing dietary recommendations is the new campaign by NCI and the Produce for Better Health Foundation (*46*) to increase the consump-

tion of fruits and vegetables through public education similar in content to that used in the statewide California program encouraging five daily servings of these foods (*37*).

This campaign might also consider new policies and programs to overcome environmental and institutional barriers to healthy eating:

1. Incentives to producers and marketers to compensate, in part, for the low added economic value of fruits and vegetables.
2. Support of farmers' markets and grocery stores, especially in low-income areas.
3. Promotion of purchase coupons for fruits and vegetables.
4. Guidelines for school lunch, food assistance, and other federal programs to promote increased use of fruits and vegetables.
5. Regulations and guidelines for institutional food-service operations (eg, in colleges, worksites, and businesses).
6. Training of food-service personnel in menu planning and meal preparation.
7. Incentives for advertising fruits and vegetables on radio and television.

These suggestions, and others, deserve serious consideration as means to encourage and enable the public to follow dietary recommendations and, thereby, reduce risks for cancer and other chronic diseases.

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# Defining and Targeting an Audience for Cancer-Prevention Messages

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**ABSTRACT—The target audience for cancer-prevention messages is not the cancer patient. Cancer-prevention messages should be designed for and directed toward groups of people who have been determined to be at risk for the disease. Potential audiences may vary widely in size and nature, depending on the specific cancer, its cause, and its etiology. The prevention of specific disease, eg, lung cancer, typically demands some behavior on the part of the recipient of a cancer-prevention message. Thus, members of a target audience may be asked to stop smoking or to refrain from starting. Each potential target audience is likely to be unique and cannot always be reached with typical mass-media campaigns. Messages designed to be effective for such special audiences may be required if a significant impact on behavior is to be obtained. This article attempts to identify potential audiences for cancer-prevention messages and develops the nature of the media to be used, the sources to be employed, and the arguments to be developed in such a campaign. Characteristics (eg, sex, race, age, marital status, and socioeconomic status) are used as examples of variables that may dictate the nature of cancer-prevention campaigns. [J Natl Cancer Inst Monogr 12:159–161, 1992]**

Scholars interested in cancer prevention and control are aware that not everyone in the population is at equal risk of developing cancer. People who smoke, eat high-fat, low-fiber diets, or constantly expose themselves to sunlight are far more likely to develop cancer than those who do not engage in such high-risk behaviors. Lung cancer, for example, may be prevented by convincing members of a population to refrain from starting to smoke or by getting current smokers to quit. In either case, the risk of acquiring cancer is reduced for the individual. Similarly, getting people to eat low-fat, high-fiber diets or to minimize their exposure to sunlight should reduce their cancer risk.

Cancer communication campaigns have usually been conducted under the assumption that, if many people are exposed to information about the risks of acquiring cancer, those people will proceed on their own to change their behavior and minimize risk. When the population as a whole is considered, this underlying assumption has been generally supported. For example, the large national campaigns to reduce smoking really began with the issue of the Surgeon General's Report in 1964 (*1*). Since then, the overall smoking rate has steadily dropped. A closer look at smoking rates, however, shows that there are subgroups in the population in which smoking rates are still high; in other subgroups, smoking behavior is still starting at far higher rates than among the general population. Clearly, current campaigns are failing to effectively reach all segments of the population. Communication researchers refer to these audience segments as the "hard-to-reach" or "resistant-to-change" groups within a society. In this article, a subgroup of the population frequently listed as hard to reach is identified and used as an example of the changes that may be necessary in prevention campaigns if we are to succeed in effectively reaching all audience segments.

## IDENTIFYING HARD-TO-REACH AUDIENCES

Although there has been a steep decline in smoking prevalence since 1964, the decline has not occurred equally across the entire population. Older men tend to smoke more than younger men, white-collar groups show lower rates than blue-collar groups, black men smoke more than their white counterparts, and young teenage women start smoking at higher rates than young teenage men (*2*). Any of these differences points to a case in which one part of a population was reached less effectively than the contrasting part. In this article, the example of teenage smoking behavior will illustrate the difficulties in planning and executing a successful communication campaign to prevent teenagers from starting to smoke.

Approximately 20% of high school senior women and just under 16% of high school senior men report daily cigarette smoking. Those figures are significantly lower than similar figures from 1977 but are still high enough to warrant further examination. Because teenage women have higher rates than teenage men, I concentrate on the teenage women of the population.

It is obvious that not all teenage women start to smoke, because most of this group is not at risk for smoking behavior. The first step in planning a campaign designed to impact the 20% of teenage women who are at high risk for initiating smoking is to further identify the characteristics of this subpopulation. There are no national data available that allow easy isolation of this group from the 80% of teenage women who are not at high risk for smoking. Instead, studies that have been conducted with small populations (ie, phase I and II studies; *3*) must be used and the larger audience extrapolated from them.

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Without trying to identify and analyze each of the many studies involved, the following generalizations seem justified as ways to better identify the at-risk group. Teenage women who are at risk for smoking

1. Tend to have parents and/or older siblings who smoke.
2. Are more likely to come from low-income homes.
3. Are more likely to come from one-parent homes.
4. Are likely to have low educational aspirations and tend to leave school before completing high school.
5. Tend not to be in the "in" crowd in high school.
6. Tend to go to work at menial jobs early in life.
7. Tend not to take part in athletics, clubs, or other extracurricular activities in high school.
8. Tend to leave home early.
9. Tend to get married at a younger age than women who do not start smoking.

There are certainly other characteristics that might further help to identify this high-risk group, but the markers listed should provide enough information to begin constructing a cancer-prevention campaign aimed specifically at this subpopulation.

## DESIGNING A COMMUNICATION CAMPAIGN

There are two major problems associated with the design of any communication campaign. First, a decision has to be made about the channel that will be used to reach the target audience. Second, a message must be constructed that will have an impact on that target audience.

Communication campaigns typically make use of combinations of face-to-face and mediated channels of communication. A typical face-to-face channel might use messages delivered at schools, churches, worksites, clubs, and other community gatherings. Face-to-face communication tends to reach fewer people and be more expensive than various mediated channels, although it may also be more effective. For the subpopulation of teenage women at high risk for smoking, these channels are probably not going to be easily identified and used. This subgroup does not tend to attend church, is frequently absent from school, does not belong to clubs, and does not value worksite programs. Face-to-face campaigns have been shown to be effective for many target audiences, but the group in question is likely to be far less reachable than other elements of the population.

If face-to-face channels are inappropriate for this situation, mediated channels must be considered, including television, radio, and the various print media. To ascertain whether one or more of these channels is appropriate for an audience, various exposure indices must be consulted. When the behaviors of the target audience are examined, the general use of print media can be rejected because teenage women at risk for smoking behavior are not regular newspaper or magazine readers. They do, however, extensively use both television and radio. The data available for either television or radio do not pinpoint the target group I am discussing; thus, it is necessary to interpolate from several indices to better isolate the at-risk group. For the entire United States, teenage women, when considered as a group, watch television more than 21 h/wk (*4*). However, households with incomes under $30 000/y spend more than 52 h/wk watching television. This contrasts with households with incomes over $60 000/y, in which only 46 h/wk are spent watching television. This suggests that my target group of teenagers is likely to spend more time watching television.

A similar pattern emerges with radio listening. The average teenage high school student spends almost 23 h/wk listening to radio (*5*). Radio-listening frequency is higher for low-income than for high-income listeners. Thus, the target group of teenage women at high smoking risk probably has a combined television and radio use of significantly more than 50 h/wk. A combination of television and radio seems to be an appropriate medium to carry smoking-prevention messages.

At least one further decision is required before a campaign message can be designed. There are many different outlets for both radio and television in every community. The number keeps increasing and makes the task of selecting a particular station or channel more difficult. In 1985, for example, only 19% of all homes had as many as 30 television channels available for use. By 1989, 51% of all homes had 30 or more channels available. Similarly, between the AM and FM bands, most communities have a dozen or more different radio stations available, each with different formats aimed at different sections of the listening audience.

In the past, many prevention campaigns made primary use of public service announcements (PSAs) to approach audiences. A short (30-s to 1-min) "spot" message was prepared and sent to local stations and network channels. The stations were urged to play the PSA without compensation. Although some stations gave excellent placement to PSAs, others did not. Almost every organization has had their PSAs played at 3 AM, after the campaign was over, or not at all.

The role of the generalized PSA must be reconsidered when discussing hard-to-reach groups, eg, teenage women at risk for smoking. These hard-to-reach groups are not likely to be attracted to the shows that most viewers watch. When there were fewer channels, and relatively fewer stations were available, the viewer had little choice; however, many choices are now available. The most-watched regularly scheduled network program is "The Cosby Show," which was seen by just over 23% of the television-viewing households in 1990. The remaining viewing audience is divided among many different shows and channels. For example, many teenage viewers watch the music television channel MTV. The target group is more likely to watch this channel than those channels used by the major networks.

The condition is the same for radio. The target group is more likely to listen to a small station that plays a hard-

rock format than to larger stations with easy-listening formats.

The further segmentation of television and radio audiences suggests that materials must be developed that can be used on different kinds of channels and stations and that better campaign research must be done to more effectively identify the media habits of specific target audiences. Organizations and institutions will have to consider using paid advertising if some groups are to be reached. Small stations and cable systems do not have the economic resources to justify using unpaid PSAs when paid advertisements are available. At best, the unpaid materials will be shifted to the most undesirable time slots.

The considerations for choosing a medium to reach a particular target audience are the same as those needed before deciding on the nature of the message, and include 1) the information level of the target audience, 2) arguments that are likely to persuade various target audiences, and 3) effective role models for different target audiences. The first two considerations are discussed elsewhere (*6*); the third consideration requires undertaking formative research that should take place before attempting to reach a particular target audience.

Almost all cancer-prevention messages use role models in one form or another. The entire message may be presented by someone deemed to have high credibility for the audience (*6*). In recent years, former Surgeon General C. Everett Koop has been asked to be the spokesperson for several prevention campaigns. Research has shown that Koop had a high recognition level and was regarded as a highly credible source of information about health. Similarly, actress Brooke Shields appeared in a nonsmoking PSA several years ago; again, research showed that she had a high recognition level for teenagers and was an appropriate role model for this general audience.

Although it is relatively easy to select appropriate role models for the general audience, it is frequently difficult to select role models for the special target audience addressed in this article. It is unlikely that either Koop or Shields would be credible role models for teenage women at high risk for smoking. The specific media frequented by this group (ie, movies, television shows, and radio programs) suggest that more effective role models could be drawn from popular rock music groups. Only careful formative research will help isolate potential role models for these difficult-to-reach audiences.

## CONCLUSIONS

Cancer-prevention campaigns have typically been designed to reach the largest groups within the society. As such, they have been effective in reducing smoking rates, changing attitudes toward diet, and raising the general information level about cancer; however, current campaigns have left some large segments of the population unaffected by the messages. To be more effective, a better understanding must be reached of population subgroups that still remain at high risk for cancer. The media habits of these subgroups must be understood to select appropriate channels to carry cancer-prevention messages, and credible role models need to be recruited as spokespersons to carry cancer-prevention messages.

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# Communicating Cancer-Prevention Information

Jane E. Brody[1,2]

**ABSTRACT—The message to the public regarding cancer prevention should emphasize moderation and evolutionary change in living habits rather than revolutions and focus on total life-style not just individual factors. It is essential to keep people focused on the modifiable factors that can really make a difference. Currently, people worry about minutiae, ie, possible substances in the environment that might cause some cancers, rather than the main, more clearly defined factors, eg, smoking, diet, and sedentary living. The media must play a major role in cancer prevention, assisted by rational, clear-speaking professionals. [J Natl Cancer Inst Monogr 12:163–164, 1992]**

Almost daily, the media proclaim another everyday substance to be a cancer risk. If people are not felled by radon in air and water, hormones in meat and poultry, pesticides on fruits and vegetables, PCB in fish, the caffeine or decaffeinating chemicals in coffee, or the colorings on jelly beans, chances are the electromagnetic waves from hair dryers or electric blankets will assault them. Why, in the face of all these hazards that people can do little or nothing about, should individuals stop smoking, cut down on fats, eat more fruits and vegetables, stay out of the sun, have Pap smears and stool examinations for occult blood, or practice any other cancer-preventing measure? With so many people already thinking that since everything causes cancer, they will do what they please, it makes much more sense for those interested in communicating health-promoting information to focus on what are likely to make the biggest differences in cancer risk, particularly measures within the control of individuals.

My primary job as the Personal Health columnist for *The New York Times* is to promote health not report news, although I am occasionally asked to report breaking developments in medicine. Most of my colleagues in science and medical writing are strictly reporters of news, and any new finding of a potential cancer hazard is fair game for daily journalists. Most journalists try to put such discoveries into perspective, but the public does not always respond predictably. For example, in an article on the relative risks of various commonly encountered mutagens and carcinogens, I wrote that, although raw mushrooms contain a natural carcinogen, eating two raw mushrooms per day is no more hazardous than eating a peanut butter sandwich. This prompted some readers to exclaim with horror about the dangers of peanut butter, most of which is eaten by young children, rather than to accept the possible risk of eating mushrooms.

Similarly, during the peak of the mammography controversy about a decade ago, I wrote on the known benefits and hypothetical risks of mammography. Although I worked hard to produce a balanced article, when read objectively, the conclusions clearly favored mammography. However, judging from my reader mail, those who had initially favored mammography were relieved by what they perceived to be my belief in its safety, and those who originally thought mammograms were dangerous believed that my article had validated their views. In other words, people read into the news what they want to hear. They also tend to fret far more about hazards they feel are inflicted on them from without rather than those that are self-inflicted. In fact, other than stopping smoking, which has many other attendant risks besides cancer, there are few personal habits that have been significantly modified when a potential carcinogenic hazard was brought to public attention.

Perhaps the most blatant example of this lack of action was the public response when the US Food and Drug Administration declared saccharin a carcinogen and intended to banish it from the food supply. All the sugar-free drink junkies of America, who obviously were far more worried about their sweet tooth and figure than their chances of dying of cancer, jumped onto the saccharin bandwagon and rallied to keep this carcinogen in their lives—even feeding it to their innocent children. The joke is that there is no scientific evidence that consuming artificially sweetened drinks or foods helps people lose weight and keep it off. In fact, on average, the people who drink sugar-free drinks are fatter than those who do not. As artificial sweetener sales soared, Americans got even fatter and ate more real sugar. Evidently, artificial sweeteners perpetuate a sweet tooth; they do not cure it.

Those who determine what gets published and what gets broadcast with respect to preventable cancer risks should be far more selective in what messages are transmitted to this schizophrenic public. In fact, *The New York Times* wrote almost nothing about Alar, publishing only a small article inside the paper after the Associated Press had broken an embargo on the Natural Resources Defense Council report proclaiming Alar to be the most important cancer-inducer ever to reach children's lunch boxes.

The media should also be more selective in judging the quality of the science that purportedly links a common substance or habit to cancer. For example, I refused to write up a Harvard study that linked coffee drinking to cancer of the pancreas because the finding had no other

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epidemiological, clinical, or laboratory support. I was proud of my decision when, several years later, the Harvard researchers themselves declared the link to be statistically invalid.

Communicators should be focusing on three themes:

1. The well-established cancer risks that are solely or largely within the control of individuals, including cigarette smoking and other forms of tobacco use, excessive consumption of alcohol, undue exposure to solar radiation, and unnecessary exposure to medical radiation.
2. Habits within the control of individuals that may cause or contribute to cancer risk as determined by considerable epidemiological and/or experimental evidence, including a high-fat, low-fiber diet, the inappropriate or careless use of exogenous hormones, and undue exposure to household radon.
3. Life-style factors strongly suspected of influencing cancer risk that would be beneficial even if they turn out to have no direct impact on a person's cancer risk, including frequent consumption of vegetables and fruits, especially those rich in $\beta$-carotene and cabbage-family vegetables, and getting regular physical exercise.

What methods of communication should be used? Providing information about avoidable cancer risks is not solely, or even primarily, the job of mass media. The media's main job is reporting and interpreting news, although judging from the success of my column, the many health newsletters, and various television specials, there is a growing audience for health-related information that is perhaps not so new but increasingly relevant to people's lives. Certainly, more newspapers and nearly all the mass-circulation magazines now have at least one column designed to put health information into perspective and motivate people to take better care of themselves.

It is up to health professionals to see that these publications and broadcasts receive sound scientific information and well-considered comments based on real evidence, not speculation or hysteria-mongering possibilities. In the last two decades, physicians and scientists have made great progress in their willingness and ability to communicate with the media, but more can and should be done. Every major medical organization and medical research institution should gather a coterie of experts willing and able to talk to reporters, and the public information officers of these groups should make their phone numbers available to local media and to national newspapers, magazines, and radio and television networks.

The media also need more support in the workplace. As medical insurance crises strike major employers, companies are getting wise to the economics of health promotion and disease prevention among employees. Periodic health-promoting checkups and guidelines are no longer solely the purview of the highest-paid executives. However, employers must also facilitate good health practices by banning smoking; offering tasty, attractive, healthful selections in the company cafeteria; discouraging excessive use of alcohol; and establishing programs to help people make the more difficult changes, including adjusting their diets and adopting regular exercise.

Of course, national organizations concerned with the public's health must continue and expand their roles in presenting sound health-promoting information to the public. The US Departments of Agriculture and of Health and Human Services have come a long way; even the attenuated dietary guidelines are better than no guidelines. However, the US government on one hand says, "Don't smoke," and on the other supports the growing and advertising of tobacco. The US government says, "Eat less fat and cholesterol," and then feeds cheese and ice cream to schoolchildren. The US government is slow and unduly subject to industry and public pressures in cleaning up cancer-causing pollutants and banning carcinogenic foodstuffs and in making useful information available to the public.

In presenting a message of cancer prevention and health promotion, it is important to avoid a "quick-fix" mentality. It is also important to emphasize that healthful living is not an all-or-nothing phenomenon. Besides tobacco, nothing must be abandoned forever. A healthy life is not a life of constant deprivation and self-denial. Rather, it is one of moderation, with occasional optional forays into "the forbidden." Most unhealthful behaviors should be modified gradually. In adopting a more healthful diet, for example, I suggest that people change one meal every week or even every other week. By the end of a year, they will have a new way of eating and will be less likely to miss the old not-so-healthy eating habits.

I am optimistic about the public's ability to act in a cancer-preventing manner. Considerable changes have already occurred and will continue to occur. Perhaps the most significant change has been the turnabout in public attitudes toward smoking. I predicted, in *The New York Times* in the early 1970s, that smoking was on its way to becoming a socially unacceptable habit and that ashtrays would go the route of spittoons. I am pleased to have lived to see this happen. Similar action now needs to be taken with regard to alcohol abuse, solar radiation exposure, fat consumption, and sedentary living.

Although only a small percentage of the population is now making a significant effort to live more healthfully, these people are the prime movers of society. The educated middle class sets societal trends, and just as this group made it popular to smoke cigarettes; eat lots of meat, cheese, and eggs; and sport a "healthy" tan, they are now promoting the opposite. Eventually, the general populace will follow, and if the medical care system does not collapse first, people will eventually be healthier, if not immortal.

# Roundtable Discussion: Where Do We Go With the Facts?

**Kenneth Warner (Moderator),[1] Gregory Connolly,[2] Michael Pertschuk,[3] *and* Nigel J. Gray[4]**

This roundtable discussion evaluated the facts regarding cancer prevention and identified critical priorities that must be addressed to translate this knowledge base into action. To set the tone for this roundtable, the moderator stressed that behavior changes as well as policy changes are equally important in implementing an effective cancer-prevention agenda.

Roundtable participants highlighted the factual data regarding cancer prevention that is available in several discrete areas: smoking, fat consumption, and sun exposure. It has been widely believed that increased cancer risk behaviors generally accepted by the scientific community have not been widely recognized or adopted in public health policy throughout the world. This single factor indicates that additional prevention and policy research is needed to identify and overcome barriers to the integration of prevention factors.

Fundamental to future research in these areas is the need to address key questions about the process of changing attitudes and changing behaviors in populations at risk. Participants urged increased resources for funding cancer prevention within the broader context of funding for cancer research.

Some initiatives identified by the roundtable participants included the following:

1. Effectiveness of media campaigns as public education tools
2. Behavioral research initiatives in special populations, including minorities and women
3. Techniques used by the tobacco industry to undermine community institutions that would otherwise help mobilize communities against tobacco
4. Techniques that transnational tobacco companies have used to integrate themselves into the economic and political systems of Third World countries.

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# Roundtable Discussion: Where Do We Go With the Maybes?

**Peter Greenwald (Moderator),[1] Maureen M. Henderson,[2] Douglas L. Weed,[3] *and* I. Bernard Weinstein[4]**

This roundtable discussion provided a forum for discussing promising research for future intervention to prevent human cancers. After presentations by the roundtable members, the audience participated in an open discussion, highlights of which are summarized.

Greenwald posed several questions for this roundtable discussion. How do we build cancer prevention into the mainstream of major research institutions? In what format and how best can we do that job? How do we get good scientists and supporters involved in this effort?

It was recommended that the most critical factor in creating opportunities for cancer-prevention research was the establishment of an extensive, multidisciplinary effort that includes behavioral science, laboratory science, molecular biology, epidemiology, and clinical prevention trials. This collaborative environment would meld diverse research initiatives and integrate critical research components to achieve success in cancer prevention.

The breadth of cancer prevention is vast, covering issues from tobacco control, nutrition, and environmental carcinogens to molecular genetics and the economics of cancer. In essence, the scope of cancer prevention covers nearly all human endeavors, including the artistic skills that go into its advertising and its ethical implications.

One of the gaps that exists in cancer-prevention research efforts is the training of graduate and postdoctoral students. Lack of trained personnel is a barrier in our ability to mount an effective cancer-prevention research effort. Current efforts under way in this area include training programs in the principles and practices of cancer prevention and control through basic and applied research activities, academic courses, and field training experience. However, at the international level, resources are not available to adequately support this initiative.

The team approach to addressing cancer prevention is crucial to our efforts to educate the public and encourage them to be responsible in incorporating cancer-prevention practices in their life-styles. It is imperative that the exciting revolution in cellular and molecular biology be incorporated into the field of cancer prevention, that epidemiologists become educated in the frontiers of molecular biology, that molecular biologists understand clinical disease, and that these disciplines work in a unified strategy to mature our cancer-prevention efforts.

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# Closing Address

C. Everett Koop[1]

I am now supposed to summarize what has been presented in these proceedings in some encapsulated form and with great erudition and send you home with an agenda that you will feel comfortable in working out. If I were still surgeon general, I am sure you would also expect me to finance what you plan to do in the future.

We should have anticipated that there is solid agreement on the facts and on the rumors. I presume we would each fit some place in a bell-shaped curve if we were to take a vote when it came to the maybes, which is as it should be.

I would like to make a few remarks about the roundtable that discussed the facts: the use of tobacco causes disease. As much as we criticize our success in the antismoking endeavor, I think that we have to recognize that, from a public health prevention point of view, it probably is the centerpiece, the showcase that we have to offer. Therefore, I think we should examine it carefully: see what we did along the way that was commendable and successful, what we did that might have impeded our progress, and then use that information as we plan to attack other problems in prevention that still lie ahead.

As one who battled both the tobacco and alcohol industries for 8 years, in reference to alcohol we are now about where we were with tobacco about 20 years ago. We are also much earlier on the curve when it comes to nutrition.

In discussing ways and means of continuing our attack on tobacco, a premise for our discussion was that we are reasonable, ethical, honest people. We talked about others who support unhealthy behavior as though they might react in the same way that we would under the same circumstances, which really is not so when it comes to money. We must recognize that we are dealing with people in the tobacco marketplace who, to accomplish their ends, can, at times, be sleazy, impolitic, colonialist, racist, and chauvinistic; many of them will stop at nothing to improve the bottom line. We have to recognize that they are probably the epitome of what we call the depths of the human condition. If we recognize that, we have some idea about the kind of hostility that we face. Within ethical bounds, we should not be timid about bringing every single weapon we have to bear on this problem.

We have studied the wiles of the tobacco industry. It is now necessary that we expose them at the grass roots, where all of the endeavors and promotions that Blum discussed can be fought. The audience, the spectators, who are being cajoled by the tobacco industry, have a right to see the other side.

One roundtable talked about maybes. It was clear that the maybes either become fact or they drop down to the level of rumors. However, if they do the latter, I do not think we can be complacent about them and ignore them.

Perhaps we have our greatest obligation to the rumors. First, we have an obligation not to let them start. I know that is difficult, but it should remind us that we have to be careful, especially when dealing with the media, to maintain balance and some sort of perspective. Second, we have an obligation to stop, qualify, or guide rumors in the right direction. I would not prescribe what those methods should be to readers of these proceedings. We also have an obligation to impart, to anyone who will listen, that rumors about cancer prevention—or indeed about any other preventive public health measure—undermine the usefulness of the facts. What I mean is that the public can get into an uproar over issues such as Alar on apples or amalgam fillings in six Canadian sheep. By so doing, they satisfy two basic human needs. One is the need to take action to protect oneself; the other is the desire to do something bigger: to join a cause and try to make a difference.

Such endeavors, based on rumors, not only prove futile in the long run but also lead to a false sense of satisfaction and actually take time, attention, and resources from preventive measures that are indeed facts, that have been tried and are true. In other words, by being very active in the wrong direction, they miss the opportunity to take a smaller action in the right direction that might be beneficial to both themselves and society.

The communication effort is something we could discuss forever. Health coverage in the media is no longer just the reporting of news. Science and medicine, therefore, have to form a much better alliance with the media than we currently have. Brody alluded to this in passing: when the Alar story broke, if a conditioned reflex had existed on the part of reporters consisting of nothing more complicated than a call to a friendly expert, a whole misinformation campaign could have been avoided, and the apple crop and much more could have been salvaged.

I would like to think that the International Council for Coordinating Cancer Research (ICCCR) has another role to play in the future. It could look to education of medical and scientific media representatives on the subject of risk assessment. This could be in two segments, the second much easier than the first.

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The first would be to try to teach scientists to communicate clearly, articulately, and with a sense of balance and priority. It would be much easier to teach risk assessment and risk-benefit ratios to those reporting the kind of scientific information that we send to them. If I were now surgeon general, I think I would make this year's project some kind of an effort to take a real definition of risk assessment to the public. The ICCCR could do that.

A sage once said that moderation is the name of the game, provided that one uses it in moderation. This certainly pertains to the dietary issues discussed in these proceedings and applies to dietary prevention more than to anything else that we have addressed.

Nutritional science is fuzzier at the edges, perhaps, than we would like it to be. It does, at times, purport to be a more exact science than I believe human frailty will ever let it be, because of the many instances we face that depend on patient recall. Because of this, there always will be difficulties in transforming nutritional surveys into hard science.

Furthermore, dietary opinion and practices are strongly held; they are not easy to change, because change is unpleasant to the dieter. The dieter also recognizes that there could not possibly be as many experts as there seem to be advising what should be eaten for the benefit of health. Another factor is that every dieter, like every smoker, has been through one or more experiences of failure. We sometimes tend to place too heavy a yoke on the person whom we are trying to help in reference to a change in dietary habits.

I have realized that there are not only diseases of the body but also diseases of society. The most serious disease of society is poverty. In this kind of forum, we cannot address that issue. However, it is important that we recognize its presence and remember how much poverty can be a barrier to the success we seek. Even though we recognize these things, we sometimes forget the social mores that are so important. We recognize, for example, that in the smoker we deal with an addicting drug, nicotine; however, we sometimes forget how difficult it is for simple things such as sociability, prestige, and acceptance to prevent changes in dietary habits.

Illiteracy accompanies poverty, so we must use methods other than literary forms to communicate, leading me to my last point. Bettinghaus was right that the messages must be delivered to target audiences, but they have to be culturally acceptable. Having delivered messages to target audiences—those who thought I was credible and those who did not—I have come to believe that public service announcements are not what young people listen to. I am convinced that our messages have to be a part of sitcoms, plays, songs, or messages such as on MTV. It is imperative to target groups not in the way they expect but almost subliminally through the entertainment they seek.

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